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DISORDERS OF CONTEMPORARY SOCIETY AND THEIR IMPACT ON MEDICINE *

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AN invitation to talk to the leaders of my profession in your great country seemed an opportunity to discuss a matter that has long interested me and may, I hope, also have interested you. For a long time it has seemed to me that many of the ills from which our profession suffers today are merely symptoms of more generalized disorders of society as a whole. Since many of us are concerned with the diagnosis, prevention and treatment of these local manifestations of illness, it is interesting, and in the traditions of good medical practice, to look at the patient as a whole. So that you should not expect too much from me, I think I should say that I am not a sociologist, and that my outlook on society is that of a professor of medicine, deeply interested in medical education and medical research, with some experience of public affairs relating to these limited fields, but none of private practice. Apart from this, my views are those of that highly convenient enigma, the man in the street. In so far as I have recognized these disorders correctly, I have thus first diagnosed them from their impact on medical education or medical thought, and only later recognized that they were general and not merely local disorders. I should add that my clinical experience has been gained in Great Britain, and I am not in a position to judge the extent to which similar conditions hold elsewhere.

Many of the worst ills of organization and outlook from which we suffer today in medicine are due to two quite different processes occurring in society as a whole. The first is the growth of strongly centralized administration, and of associations, trades unions or parties which impose strict rules on their members. These result in an important and, to my mind, serious disease which may perhaps be named compulsory uniformity.

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I regard this as a serious disease, partly because I cannot think that it can be to the ultimate good of mankind, and partly because it expresses extremely powerful forces which we understand dimly, or not at all, and which we have no immediate prospect of controlling. The second process is a very different one. It is the growth of science and technology. This has produced a series of relatively minor disorders, many of which we could remedy if only more of us realized the need.

Compulsory Uniformity: An urge to conform to the behavior of the rest of our fellow creatures is one of the strongest motivating forces in human affairs. This urge was first clearly defined and described by my old teacher, Wilfred Trotter, no mean achievement for a practicing surgeon, who reached such eminence in his profession that he became Sergeant Surgeon to His Majesty George V, one of the duties of this ancient office being to accompany the sovereign into battle. The herd instinct, as Trotter called it, is the basis of human society; it is the cement which binds together the family, the team, the firm, the institution, the political party and the nation. It is the basis of education by precept, since it is, fortunately, the urge of the young to imitate those whom, for the time being, they regard as their masters or betters. The herd instinct is thus a part of human behavior that we have to accept, because it is an elementary property of man. It is also a property without which civilized society as we now know it could not exist or persist.

In every country at every time and in every branch of human endeavor, there has also existed an urge to improve on nature and to force others to conform to some code of behavior. This, again, is an essential part of civilized society, finding its expression in the law of the land, and in the regulations without which no institution could for long conduct itself. And here, if you will permit me to digress, I would like to say that the reason why countries like the United States and Great Britain are such satisfactory places in which to live is because we have evolved a very reasonable system of law, and this law is enforced. If only some reasonable code of international law could be drawn up and enforced, many of our troubles would be at an end. Having mentioned the word reasonable, I would like to stress it, because it seems to me that the essence of a lively and interesting society is the absence of unnecessary rules and restrictions. Too many rules and regulations carry the penalties of producing a very stereotyped form of existence, and of abolishing initiative. Life, in fact, becomes dull, and that, I think, is tragic, because life should be such an exciting adventure. To give you an example of this generalized disorder of society, let me quote to you from a speech of Mr. Narayan, who was the heir to the leadership of Mr. Nehru in India. This quotation appeared in the Sunday *Observer* while I was preparing this address:

"There is a tendency to forget the human being. We remember groups, classes, religions. We think of the workers, the capitalists, the Asians,

the Americans, the Russians; but we forget the individual man. Humiliating Western domination has shaken the Asians' faith in their traditional ways. They have come to associate their plight exclusively with the lack of material power, and they are turning their energies ever more insistently to the achievement of such power. But in their efforts they tend to forget the human being, to over-govern, to legislate even on matters of individual conscience. And they have come, in the short years of their freedom, to accept that everything should be done through legislation."

I first became aware of what I regard as a pathologic desire to make all doctors alike some three or four years after the end of the war, when two proposals were under discussion in Great Britain. The first was a proposal in one large university to abolish one of the alternative routes which students have been able to follow for the early part of the medical curriculum. In Great Britain, boys and girls enter universities from school at the age of 18 or 19, having spent from one to four years in the sixth form, in which they may receive specialist education to quite a high level. In England, candidates who have done enough general science, and who prove it by passing the requisite examination, are excused the course in general science at the university. The proposal was to abolish this exemption and to treat boys who had done a lot of science and those who had done little exactly alike. The second was a series of proposals to lay down in detail the posts which men should hold over a period of four years before they could be eligible to hold consultant posts in the various specialties in the Health Service. A small calculation will, I hope, suffice to show you the effects of the two proposals. In Great Britain the medical curriculum lasts six years, after which a year must be spent in basic resident posts in recognized hospitals. Then there follow two years of compulsory National Service. If to this were added the four additional years prescribed in detail, as was proposed, it would have meant that for 13 years, from the age of, say, 18 to 31, the experience of all those entering a particular kind of post in the Health Service would have tended to be exactly alike. To appreciate the full significance of this, you must remember that in Great Britain there is now no career in clinical medicine outside the National Health Service. The example which showed up the folly of such proposals was mental health. In our National Health Service, mental health is the third most numerous specialty, after general medicine and general surgery. It is also the most stagnant. It would seem abundantly clear that, if progress is to be made in this difficult field, every encouragement must be given to men of original mind, and with a great variety of experience of other branches of medical science. There could be no surer method of preventing such a development than by the establishment of regulations of the sort I have described.

It is quite beyond my capacity as a sociologist to trace the causes of this excessive appetite for legislation and regulation. In Great Britain, it is no

doubt related to the concept of the welfare state which grew out of the tragedy of unemployment between the wars, and the enormous, and temporarily necessary, growth of detailed, centralized administration during the war. But there is undoubtedly a strong movement to introduce more uniformity into our educational system because, it is argued, education confers privilege, and privilege should be abolished.

Were I to give you details of the complexities of our educational system, its assets and its defects, I should I fear, probably confuse you and certainly bore you. But I would like to make two general points, which are applicable to Great Britain and may be applicable outside it. My first general point is that in education there tends to be a fundamental difference of outlook between the administrator and the teacher. The administrator is concerned with rules and regulations that apply to large numbers of individuals. To deal with large numbers, one must assume that they have certain common properties, and there is no doubt in my mind that the administrator wants to believe, and in time tends to come to believe, that all students should be more or less alike and, if they are not, then they should be made so. The educationalist, however, is interested in individuals. He delights in the exceptional creature who often has great virtues and great faults. The function of the teacher is to develop the virtues and minimize the faults of his pupil, and to direct the student into a channel of endeavor where his virtues will shine and his faults be unimportant. The conflict between the administrator and the educationalist is very similar to that between the the farmer and the gardener, between the ready-made and the made-to-measure tailor. In contemporary societies, with their huge populations and their urge to ever higher standards of living in a material sense, nothing can stop the development of standardized products of high quality in large numbers. But I would like to urge that we exercise great care lest the individual be lost in the process. And I would urge that this is particularly important in the field of higher university education, from which most of the leaders of our society and of our professions are likely to be recruited.

This leads to my second point: that there is an important issue here which Sir Richard Livingstone has called "the pursuit of the first-rate." I believe that society will be the poorer if we cease to allow, much less to encourage, that handful of rather odd creatures to fulfill their possible destiny. For most of those who make important contributions to knowledge and ideas have had rather peculiar careers. The proposed regulations to which I have referred would have prevented the late Sir James Mackenzie from obtaining a post as physician in the National Health Service, and while, as we know, his great scientific work was done in general practice, his influence on the next generation was more personal. My late teacher, Sir Thomas Lewis, himself a peculiar creature, might not have done what he did had he not fallen under the influence of Mackenzie after his appointment to the London Hospital.

Although my defense of the individual is based on educational, and particularly medical, considerations, it has wider implications of even greater importance, to which I may briefly refer by quoting Sir Geoffrey Vickers, Treasurer of the Medical Research Council, though himself a layman. The quotation is taken from an address before the World Conference of Mental Health, held in Toronto in 1954. The address is entitled "Mental Health and Spiritual Values." In it, Sir Geoffrey is concerned with relating these two worlds of thought, the spiritual and the scientific, and particularly with the extent to which progress in psychology is likely to reduce the problems that beset us, or, alternatively, to help us withstand them better. He says: "May it not be rather that we are neglecting the more important need? By all means let us reduce the occasions for stress; but stress will remain a characteristic of human life and it may be that if we could remove it, we should lose what most we need. Security is not to be found by eliminating challenge, but only in an inner assurance which no challenge can disturb.

"The easy way to relieve stress is to yoke mental science and modern techniques of persuasion to the task of making everyone well-adjusted to everyone else. This is not only tempting, it is in a measure useful and indeed necessary. For our growing organisation demands ever more conformity, ever more mutually adjusted specialism, ever more acceptance to make it work at all. There seems ever less time for doubt and for dissent. Yet both Christian and scientific insights warn us that along that road lies mortal danger not only for the individual but for society also.

"For saints, artists, creative thinkers, and above all martyrs are seldom well-adjusted people; and no civilisation can do without them, least of all ours which changes faster than any has before. These are they who incubate to-morrow's orthodoxies through their heretic phase—for all orthodoxies were heresies when they were born. These are the deviants, from among whom spiritual evolution will find the material for her next big adaptation. In every age so far enough have escaped martyrdom to fertilise the next. It would be ironic, if we alone were efficient enough to make ourselves spirtually barren."

The next group of disorders springs from the growth of scientific and technologic knowledge. If you agree with me that the disorders exist, then you will also agree that, unless we apply the appropriate remedies soon, the disorders will become serious before many more years, since scientific and technologic knowledge seems to increase in geometric progression.

The first disorder is overcrowding of the curriculum. In our country this is particularly true of medicine, technology and science. It is less true in the arts. In medicine, for example, not only new knowledge but also new subjects are constantly being added to the curriculum. Rarely, if ever, is anything taken away. The student has to work increasingly hard to cover the ground, and he learns to appreciate those teachers and

textbooks that provide him with knowledge in a form that can readily be reproduced for examination purposes. He has less and less time to devote to those aspects of civilized life which are not embraced by the confines of his curriculum. This has two unfortunate consequences. The first is educational. In the kind of teaching we give in universities, a distinction may properly be drawn between the processes of education and instruction. In education, the student is encouraged to work and think for himself; the function of the teacher is to stimulate and criticize. Education is expensive in time and effort of both teachers and pupils. But it produces the most finely trained minds. By contrast, instruction is a process whereby the student is required to assimilate a series of dicta, without inquiring into their validity or necessarily considering the evidence on which they are based. It is a process which does not necessarily improve the mind of the recipient, and may actually do harm by suppressing curiosity, insight, and the capacity to learn from experience. Now, it is evident that overcrowding of the curriculum can have only one result, namely, that education gives place to instruction. I am one of those who still think that it would be better to send out our students knowing rather less, but understanding better how to learn, for the stock of facts with which they have been equipped is a steadily diminishing asset; and if they have not learned from us how to learn, then perhaps they never will. Less obvious, but no less important, is the restriction imposed by an overcrowded curriculum on the pursuit of general cultural interests. If a student spends nearly all his day in receiving instruction and his evenings in working at his books, it is not surprising that he is all too often uninterested in art, music and literature, and in those intangible spiritual values on which ultimately any civilization rests—in fact, in the finer products of the human mind. One of the qualities that are most essential in a doctor is wisdom, and wisdom is acquired neither from instruction nor from textbooks. It is a product of two other qualities: a sense of proportion and an appreciation of ends. Both of these are qualities of the mind that can be developed only by personal experience. Personal experience requires time, which tends to be increasingly occupied with the narrower requisites of the curriculum. From the broader point of view, this would seem to me to be a serious disorder. The greatest danger to mankind arises from man himself, and wisdom is necessary today as it never was before.

The second disorder arising from the growth of science and technology may be termed the fascination of machines. This disorder is one which manifests itself with unusual clarity in the field of medicine. As year succeeds year, some new physical or chemical technic and some new and elaborate machine are applied to the study of disease; great claims are always made for the precision of the answers yielded by these technics and machines. One of the greatest struggles that a practicing doctor has is to keep up-to-date with advances of this kind. No sooner has he mastered

one than another is upon him. Moreover, the machines or technics are often so complex that he cannot understand them. He has to take what they tell him on trust. It must be within the experience of many of us that there is a growing tendency for doctors to rely on the information given by such technics and machines in preference to the information which they gain themselves from the history and physical signs. I am extremely doubtful if this is in the interests of good doctoring, and for three reasons. First, the errors and limitations of these new technics are not at first appreciated. Often the data yielded by clinical examination are of much greater precision in the identification of disease. Second, a thorough clinical examination, which will be carried out only by doctors who appreciate its worth, is the best method of establishing that spirit of mutual understanding and good will which is the core of the doctor-patient relationship. Finally, to rely on data, the nature of which one does not understand, is the first step in losing intellectual honesty. The doctor is peculiarly vulnerable to a loss of this kind, since so much of therapeutics is based on suggestion. And the loss naturally leaves him and his patients the poorer.

There is another aspect of this question which deserves a little notice. For some years it has been my privilege to visit institutions of learning with a view to deciding what financial help they need and can profitably use. There is no doubt that a collection of elaborate machinery makes a deep impression on the layman. It is necessary to be constantly on guard to see that support goes to men and ideas and not to machines.

The third disorder arising from the growth of science and technology is the fragmentation of knowledge. Existing knowledge is now so vast, and the technics that are used to win new knowledge are so exacting, that men are forced to canalize their efforts into a restricted compass. As has been truly said, we all tend to become specialists and, in so doing, to know more and more about less and less, until eventually we may know everything about nothing. As far as the practice of medicine is concerned, we are witnessing the extinction of the family doctor, and even the general physician, and their replacement by a panel of specialists among whom the psychiatrist may seem to qualify best for the rôle of guide, philosopher and friend. I am old-fashioned enough to think that something of inestimable value to the patient is lost in this process, and that there is a place for the old type of family doctor and for the general physician, as well as for the specialist. And I am glad to say that, despite the blows administered to him by the National Health Service in Great Britain, there is a new movement to establish the prestige and to define the peculiar functions of the General Practitioner or family doctor.

The other local symptom of this disorder is the steady addition to the medical curriculum of new subjects, each presided over by an autonomous professor. This process is, of course, necessary for the growth of knowledge. But, unfortunately, it tends to happen, in our country at least, that

each professor feels it his duty to his subject to see that sufficient hours are allocated to it in the curriculum, and that his subject has a separate examination in which the student must pass before he is allowed to leave that department. In my more detached moments I see these worthy gentlemen, each determined to exact his pound of flesh, as a flock of vultures descending on the student, until only the bare bones are left. And I sometimes feel when I listen to these eminent scientists that their arguments are all perfectly valid, except that they have forgotten one thing: that the subject of their improving exercises is a living, feeling and, we hope, thinking human being whose capacity to take intellectual punishment is extremely limited. Nowadays, be it in medicine, in education, in political reform, there seems to be a tendency to forget the individual.

I come now to the last type of disorder, the tyranny of scientific and technologic jargon. That this is a general disorder of contemporary society is well known, and our Prime Minister, Sir Winston Churchill, has not spared his tongue on the kind of technical jargon used in the Civil Service. But I would venture to suggest that this disorder finds its most florid expression in the world of science and technology, and particularly in the world of medicine. To begin with, it is beyond dispute that a new element or a new compound must be given a name so that men may know it; so must a newly discovered process or force, or a new disease. Much of this technologic jargon is, therefore, unfortunately necessary. It is an essential part of the growth of science and technology. But much of technologic jargon is not really necessary and could easily be discarded. Technologic jargon has two evil effects: first, it accentuates the fragmentation of knowledge; second, it facilitates confusion of mind because it tends to hide it. I fancy that all of you have had an experience similar to my own. I find difficulty in understanding what I read in some medical journals; I find greater difficulty in reading journals devoted to biochemistry, chemistry, botany, zoology or genetics, and I find most mathematical or physical journals quite impossible. Some of this difficulty is due to discoveries and ideas new since I was a student, and some to my own defective education. But most is due to the use of unnecessary technologic jargon. In creating our own jargon we are fencing off our subject so that it shall be, as it were, inaccessible to any not initiated into its technicalities. If we are interested in the growth of knowledge, and if we acknowledge, as we must, that knowledge is a whole, then we must deplore anything that accentuates this process of fragmentation. We should, in fact, demand that technologic words never be used in scientific papers if familiar words can be used instead. To give an example, I showed my colleague, the Professor of Anatomy, the following passage: "hypokalaemic hypochloraemic alkalosis was present." He had no idea what it meant. Had the statement read: "plasma potassium and chloride were diminished, CO_2 increased," he would have understood. Here the simpler phrase is

seven letters more. But editors are not always so particular in curbing verbosity. Moreover, another example from a recent paper by a very able and highly cultured author, "bilateral nephrectomy was performed," is not only less easy for a non-biologic scientist to understand than "both kidneys were removed," but is also 11 letters longer. Much of this technologic jargon is thus unjustifiable on any grounds whatsoever, and I can only regard it as a bad habit into which we all tend to fall. The other evil consequence of technologic jargon is not less important, but its ill effects are more insidious, and most of us, to a greater or less degree, are already its victims. I refer to its inhibitory effect on our own mental processes. When we use a technologic term there is a strong tendency for the idea to become isolated and inaccessible to those periodic spring cleanings to which we subject our more ordinary mental furniture. Thus, by using a technologic term we often assume an entity where in fact none exists; the next process is to invent it. Thus, by using a technologic term, we may create an artefact. An outstanding example of this is essential hypertension. The realization that this condition is not an entity but merely represents one end of a curve of continuous variation, and thus that the condition is, in a sense, an artefact, has been one of my greatest personal experiences. Certainly many of the features that were said to characterize the course of the disease, and some of the more credible hypotheses of its causation, were consequences not so much of facts but of the assumption made in interpreting them, the particular assumption made being that a dividing line could and should be drawn between normal blood pressure and hypertension. This assumption was a consequence of the idea that essential hypertension was an entity, an idea that in its turn arose from the use of a technologic term and the necessity to define it. In terms of wasted effort, the use of this technologic term must have cost medical science several thousand man years.

The second source of confusion arising from the use of technologic terms is that they may seem to be much more precise than they are, and different people using the same word may be considering totally different things. My first example, stress, is an interesting one, since it is an old word and has only recently been used in a technologic sense. Its usage in ordinary language has never been well defined. It means, in general, the application of an adverse force to an object, be it living or dead. Sometimes, however, the word is used to apply to the external force, sometimes to the process induced in the object to which the force is applied. The originator of the contemporary enthusiasm for this word was, as far as I know, Hans Selye, who observed a common pattern of response to a large number of potentially injurious stimuli. He argued that this common response implied a series of events initiated by a common disturbance, and proposed that this disturbance be termed stress. According to this concept, stress is the first stage in response to injury. Wolff used stress in the same sense as part of the response, but with the more limited meaning

that this part of the response occurs in those aspects of cerebral behavior that we call the mind. While these two eminent authors use the word in a well defined sense, the sense is different in the two cases. Moreover, others have extended its usage in the following ways: to connote actual tissue injury, or a stage short of it; to connote mental conflict; to connote a variety of environmental factors having an adverse effect on the body. I must confess that I suspect that most of those who use the word obtain by using it a glow of satisfaction through being really up-to-date; but its chief effect on me as a reader is to leave me utterly confused.

My second example is arteriosclerosis, which means no more than a noninflammatory structural abnormality of arteries. Unfortunately, it is often used by authors to apply to a specific form of arterial lesion, for example, to the fatty nodules that occur in the aorta and its large branches, or to the lesions which produce the abnormalities visible in the retinal arteries with the ophthalmoscope. The first occurs only in the largest arteries, affects the intima and is essentially lipoid in nature. The second occurs in arteries and arterioles measuring about 1/10 mm. in diameter, affects media chiefly, and consists in an overgrowth of fibrous tissue at the expense of the muscle. These two processes are totally different in every respect. Yet all too often, in scientific papers, the writer assumes they are the same, and I suppose because he uses the same technologic term for both.

I would therefore advocate two things: first, that we watch very carefully our own use of technologic jargon; second, that we not allow our students and assistants to use it unless they can explain to us in simple words what they mean by the terms they employ. If we do this, I have little doubt that our pupils will in the long run have reason to be grateful to us. My personal contacts with great scientists lead me to suppose that one of the reasons they have made their great contributions is that the ideas and images they manipulate in their minds are relatively simple and well defined and bear a close relation to reality. I would suggest that the greatest enemy to straight thinking in medicine is technologic jargon.

This account is not in any way exhaustive, and I have omitted altogether one important disorder, namely, an excessive appetite or, should I say, a perverted appetite for Committees, which is particularly rife in Great Britain.

In presenting these views, I suspect that I may appear to others, as indeed I sometimes appear to myself, a reactionary of the deepest dye. Perhaps, therefore, I should make it clear that I am not opposed to change; indeed, our profession is dedicated to effecting change. Change is, moreover, inevitable, and to try to stop it would be about as sensible as trying to empty the Atlantic Ocean with a teacup. But it will be given to all of us to contribute to the fashioning of that change, and perhaps we shall do it more wisely if we are aware of the ailments that may and do affect the body and the soul of our important patient.

SUMMARIO IN INTERLINGUA

Le studio del problemas administrative in practica, recerca, e education medical revela certe disordines. Post reflexion on arriva al conclusion que illos non es specificamente characteristic del medicina sed affice le societate contemporanee de maniera plus general. In plus, illos non es nove. Le prime de iste disordines, que pote esser definite como "uniformitate compulsori," ha essite endemic ab le origines del civilization, sed su virulentia se ha augmentate con le crescente dimensiones del gruppos social. Le secunde disordine, que resulta del crescentia phenomenal de nostre cognoscentias scientific e technologic, include varie aspectos: le congestion del curriculo, le fragmentation del information, le fascination del machina, e le tyrannia del jargon professional. Le manifestationes e le etiologia e therapia de iste disordines, in tanto que illos occurre in Grande Britannia, es brevemente considerate.

THE RÔLE OF DIET AND HORMONES IN THE PREVENTION OF MYOCARDIAL INFARCTION * †

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Introduction

The rôle of diet and hormones in the prevention of myocardial infarction is not definitely established, but the evidence available today strongly suggests that they do play an important rôle. Their effects are dependent chiefly upon four modes of action:

1. An alteration of the personality, motivation and drive of the individual, which may place undue strain upon a vulnerable vasculature and may be the immediate precipitating cause of the infarction.
2. The development of hypertension, which accelerates "wear and tear" of the coronary arteries and, in the presence of the atherogenic trigger mechanism, hastens atherosclerosis.
3. The development or facilitation of atherosclerosis, which may be followed by narrowing or obstruction of the vascular lumen either because of (a) sclerotic encroachment; (b) ulceration of the atheromatous plaque, with escape of the atheromatous material; or (c) ulceration with secondary thrombotic occlusion.
4. The development of a ready facility to thrombus formation.

I will have nothing further to say about the first and last of these, and little to say about the second, because of the press of time. Instead, I would like to concentrate upon the subject of atherosclerosis.

Considerable change has occurred in our attitude toward atherosclerosis in the decade and a half since our department began a major program of study of this disease. Atherosclerosis is now clearly delineated as a distinct entity among the arteriosclerosis. It is no longer linked in a loose, confusing synonymity with hypertension. Atherosclerosis is no longer dogmatically identified with aging. It is now clearly established that it is a disease—a disease following upon alterations in cholesterol-lipid-lipoprotein metabolism. This cholesterol-lipid-lipoprotein concept of atherogenesis is fundamental to most of the research proceeding on this problem today.

* From the Symposium on Acute Myocardial Infarction, presented at the Thirty-sixth Annual Session of The American College of Physicians, Philadelphia, Pennsylvania, April 26, 1955.

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Generic Concept of the Nature and Cause of Atherosclerosis

Recently, in taking stock of our work, we have come to adhere to an over-all *generic* concept of the nature and cause of the disease—what may be called a *polyphasic biologic-sociologic approach*. The basic elements of this approach are:

The human organism is a single biologic-sociologic entity, an integrated, coördinated, regulated, unified whole, distinct from but inextricably interlinked with and dependent upon its biologic-sociologic environment over the life span. The whole course of evolution, from the very origin of life, placed this stamp upon man. Of key importance for this adaptive integrity over the life span is its humoral-hormonal-neural mechanism for internal and external coördination and regulation.

In advancing this polyphasic concept of the causation of this disease, we must bear in mind the distinction between *etiology* and *pathogenesis*. Multiple stimuli seem to play a rôle in the *etiology* of atherosclerosis. These stimuli all appear to lead to the same end result, because in one way or another they elicit a single basic pathogenetic response pattern. Hence, recognition of the polyphasic *etiology* of disease does not negate the possible validity of the cholesterol-lipid-lipoprotein metabolism concept of the *pathogenesis* of atherosclerosis.

This general viewpoint leads to a valuable type of investigation of this disease, which can take its place alongside those of the clinic and laboratory. I am referring to the ethnopathologic, epidemiologic method of medical chronology and medical geography.

The first cardinal fact demonstrated by ethnopathologic research is that the incidence of atherosclerosis varies significantly among different peoples. These differences almost certainly cannot be attributed exclusively to race, nationality, genetic constitution, climate or geography. One factor possibly conditioning the variable incidence of hypertension, and perhaps atherosclerosis itself, may be the general life situation, its pace, attendant stress, influence on temperament, etc.

The second fact clearly emerging is the decisive rôle of diet in determining the *variable* incidence of atherosclerosis in time and space. Thus, as long ago as 1934 it was possible (on the basis of 28 reports in the literature) to conclude that atherosclerosis is absent in no race with a recorded high cholesterol intake (in the form of eggs, butter and milk) and a high fat intake. And atherosclerosis is not prevalent in those races which consume a high protein diet—which naturally contains small quantities of cholesterol—and in which the neutral fat intake is low. A review of the recent literature has yielded ample further documentation supporting this conclusion—including data on white and Negro North Americans, Africans, British, Ceylonese, Chinese, Costa Ricans, Eskimos, Italians, Japanese,

Okinawans, Scandinavians and Spaniards. It further revealed that population groups ingesting a diet low in cholesterol-lipid over the life span are not only remarkably free of atherosclerosis but also exhibit remarkably low plasma cholesterol levels (in terms of American "normal" values). In contrast, population groups ingesting a diet rich in cholesterol-lipid over the life span manifest a tendency for plasma cholesterol to rise postnatally, remain at an elevated level in the early decades, and rise further in the later decades. Such population groups invariably experience an extensive morbidity and mortality due to atherosclerosis. However, when such groups are compelled to abandon their life-span dietary habits for a significant period of time (e.g., the European experience during World War II), the tendency to atherosclerosis is reversed, and the trend of plasma cholesterol levels is downward.

These incontrovertible, highly significant facts decisively reënforce the validity of the conclusion that the level of cholesterol-lipid intake over the life span is a key factor influencing human atherogenesis, and stands today as one of the major pillars of the cholesterol-lipid-lipoprotein concept of atherogenesis, as well as one of the decisive guides for laboratory and clinical research on this disease.

It should be noted that the present-day "normal" American diet—rich in cholesterol-lipid (derived in large measure from dairy and poultry products)—is (in terms of both biologic and sociologic human phylogenesis) a relatively recent innovation in nutrition. This is a diet of civilization—a diet markedly different from any ever consumed by wild animals or by primitive food-gathering peoples. It may well be a remarkable example of the validity of the thesis that ". . . civilization, by removing man from the natural rhythm of life, by creating new and artificial conditions, often produced new causes of disease. Nutrition, clothing, housing, all designed to protect man against environmental injuries, have also, when inadequate or wrongly approached caused illness, even created new diseases." (Sigerist, H. E., cited in reference 4).

Prior to the neolithic mastery of food production, a diet like ours today was impossible of achievement. Moreover, since the dawn of civilization in the Fertile Crescent, only small proportions of the people of the world have been "privileged" to enjoy such luxus diets. This remains true right down to the present in most parts of the world. In the economically underdeveloped countries of Latin America, Asia and Africa, malnutrition and infectious diseases remain the major public health problems. The life span continues to hover around the 30-year mark. Obviously, the decisive biologic-sociologic prerequisites are absent for the emergence of atherosclerosis as a major epidemiologic problem, and the fact is that it is not a significant health problem in these countries. Thus, up to the present the problem for the overwhelming majority of mankind in most of the countries of the world has been the stress of malnutrition over the life span, not the stress of overeating. In the United States and several other economically developed

Western countries, however, the latter problem has recently emerged in full force (even though malnutrition is not yet fully vanquished).

The bulk of present-day evidence indicates that man, as a species, has not phylogenetically acquired the ability to adjust perfectly to the new luxus diet, any more than he is able to thrive in optimal health and achieve an optimal life span on an inadequate diet.

In marshalling these facts and concepts about the relationship between diet and one of the cardinal cardiovascular diseases, it is essential to be wary of any oversimplified idea that atherosclerosis is merely a problem of diet, pure and simple. Rather, the approach to the rôle of diet must be that of the polyphasic biologic-sociologic concept of the causation of disease, since any attempt to account for atherosclerosis via a "single cause" dietary explanation must do injustice to the facts of life.

This is readily revealed when this disease is analyzed biologically and sociologically as a phenomenon of groups (in contradistinction to the clinical approach of studying individuals). Thus, it would be relatively simple to select a group of 1,000 American males, age 40 or 50 or 60, who over the life span have ingested a typical American diet high in cholesterol-lipid and calories. Despite essentially identical patterns of food ingestion, marked individual differences would be present within the group in morbidity and ultimate mortality due to atherosclerosis (although over 90% would exhibit gross anatomic evidence of this disease). Who among us is not familiar with the octogenarian who, morning, noon and night for 80 years or more, has been eating ham and eggs (or their equivalent), spiced with generous additions from the salt shaker—with apparently complete cardiovascular immunity! And who among the males in medical research is not jealously and painfully aware that the so-called weaker sex possesses a remarkable relative immunity to coronary atherosclerosis in the premenopausal decades. These individual variations can hardly be attributed to dietary differences. However, lest such facts lead us to the erroneous conclusion that diet has nothing to do with atherosclerosis, let us also remind ourselves that among 1,000 males in another population group (e.g., the Bantu or Okinawans) atherosclerosis would be as remarkably infrequent at age 40, 50, or 60 as it is frequent in our 1,000 American males. These group differences are almost certainly attributable in large degree to differences in diet over the life span, particularly differences in cholesterol-lipid intake.

The ingestion over the years of a diet rich in cholesterol-lipid is an *essential prerequisite* for the development of significant atherosclerosis in a population group. Such a diet may be regarded as an essential "trigger" for the atherogenic process (viewed as a group phenomenon). Once the trigger is pulled (i.e., once the prerequisite diet is ingested), individual differences—endogenous factors (hereditary, constitutional, etc.)—come into play to influence whether the charge is fired (i.e., whether the given person develops significant atherosclerosis). More specifically, the humoral-

hormonal-neurologic mechanisms, which integrate and organize man's relationship with his nutritional environment, play a key rôle in determining whether disease develops. Actually, the interrelationship is undoubtedly more complex, in that not only does the nature of the given organism's integrative mechanisms influence the response to diet, but the diet in turn influences the organism's integrative mechanisms and their endogenous response to diet over the years. Some facets of these complex interrelationships between organism and environment are currently being explored *in extenso*. It may be safely predicted that research along these lines will ultimately delineate the detailed mechanisms of those pathophysiologic interrelationships between organism and diet which are decisive in the pathogenesis of atherosclerosis.

Experimental Studies on Chickens

This over-all approach to research on the pathogenesis of atherosclerosis has developed with increasing clarity in our laboratory in recent years, to become the explicit theoretic foundation of the department's program of investigation on this disease. As a consequence, our main line of endeavor has been experimentally to delineate aspects of the interaction between diet and organism in the development of atherosclerosis. The general design of experiments has been to analyze the experimental animal's response to different diets under conditions of controlled variations in the endogenous function of the organism. In keeping with the concept that attention must be focused on total organism—total environment interrelationships over the life span—emphasis has been placed on chronic experiments utilizing intact animals.

The cholesterol-lipid-lipoprotein concept of atherogenesis has a firm supporting pillar of evidence from experimental pathology. Experimental atherosclerosis has a prehistory and a history. Prior to 1910, many investigators attempted to reproduce the lesion of human atherosclerosis in experimental animals—without success—by a host of means. Various arterial lesions were induced, but not atherosclerosis. Positive results were obtained for the first time in 1910–12 by feeding rabbits cholesterol-containing tissues or pure cholesterol in oil. This achievement of Anitschkow and co-workers instituted the dawn of experimental atherosclerosis. It stimulated two decades of intense research activity on cholesterol-induced atherosclerosis in rabbits. However, this investigative effort fell short of achieving a solution of the problem, and a mood of skepticism arose in some quarters, based primarily upon two criticisms arising from the work itself. The first: Cholesterol-fed rabbits—in marked contrast to most atherosclerotic patients—exhibited gross hypercholesterolemia and generalized tissue cholesterosis. The second: Little or no success resulted from attempts to induce atherosclerosis by cholesterol feeding in laboratory species other than the rabbit. Therefore, some investigators argued, the findings

in the herbivorous rabbit (subsisting normally on a diet devoid of cholesterol) were exceptional and irrelevant for clarifying the problem in man.

It was this situation that stimulated Dauber and me to undertake studies in an omnivorous species, the chicken, when we launched our program of atherosclerosis research a decade and a half ago. In the intervening years, both of the foregoing objections have been shown to be invalid. In rabbits and chickens, it is possible to produce gross atherosclerosis with minimal hypercholesterolemia and organ cholesterosis, simply by proper manipulation of the time-dosage course of cholesterol feeding. Moreover, as a result of the efforts of several groups, atherosclerosis has now been successfully induced in practically every laboratory animal species, invariably by altering cholesterol-lipid-lipoprotein metabolism and effecting hypercholesterolemia, through dietary means alone or combined with changes in endogenous metabolism (e.g., hypothyroidism, nephrosis, protein deficiency).

With the demonstration that atherosclerosis could be readily induced in chicks by cholesterol feeding, experiments were quickly devised to quantitate the atherogenic process in terms of amount and duration of cholesterol feeding, degree of hypercholesterolemia, etc. Once controlled quantitation was achieved, it became possible to analyze the long-term effects of various exogenous and endogenous factors on atherogenesis. The general design of experiments has been to feed chicks a cholesterol-lipid-supplemented atherogenic diet and simultaneously to vary exogenous or endogenous factors influencing the organism. In the main, the effects of two general types of intervention have been studied: (1) variations in dietary factors accompanying the atherogenic regimen; (2) alterations in endocrine function. Time does not permit a comprehensive survey of the many experiments.

With respect to dietary factors influencing response to a cholesterol-containing, potentially atherogenic diet, it may be briefly stated that significant changes in hypercholesterolemic and atherogenic response of chicks were effected by chronic undernutrition, withdrawal of neutral fat, addition of excessive neutral fat, supplementation with plant sterols or a defatted brain extract. In contrast, numerous so-called lipotropic factors—choline, inositol, pancreatin, activated whole pancreas, anti-fatty liver factor, tocopherols, vitamin B_{12}, lipocaic, etc.—were without influence on hypercholesterolemia and atherosclerosis in cholesterol-fed intact or depancreatized chicks. These negative results are completely in agreement with those of other workers studying other laboratory animals and man. The fact that lipotropic factor supplementation of a generally *adequate* diet failed to influence atherogenesis in no way contradicts other observations that choline deficiency induced arterial, myocardial and renal lesions. On the basis of clinical and laboratory studies, there is no justification for the widely advertised claims of some pharmaceutical houses that their proprietary lipotropic factor preparations are of value in the prevention and treatment of human atherosclerosis.

On the basis of many leads from clinical, laboratory and ethnopathologic research, particular attention has been given in our investigative program to the influence of variations in endocrine function on the organism's response to a potentially atherogenic diet. Studies have been accomplished on the chronic effects of thyroid, gonadal, pancreatic, anterior pituitary and adrenal cortical hormones. In this presentation, the results of this approach and program are reviewed only insofar as they relate to two key questions posed by the clinic: (1) Why are diabetics afflicted by accelerated intensified atherogenesis? (2) Why are men (in contrast to women) preferentially victimized by atherogenesis in the prime decades of life?

Experimental Diabetes Mellitus

One of our earliest experiments bearing upon the diabetes problem involved analyzing the effects of alloxanization or pancreatectomy in cockerels. Unfortunately, these chicks exhibited no signs of diabetes; they manifested no derangements of either carbohydrate or fat metabolism. When fed a mash supplemented with 0.5% cholesterol plus 5% cottonseed oil, their cholesterolemic and atherogenic response patterns were identical with those of the intact controls. The same negative results were obtained with a 2% cholesterol diet. However, when a more highly stressful dietary regimen (2% cholesterol plus 5% cottonseed oil mash) was fed, the pancreatectomized cockerels exhibited moderate intensification of hypercholesterolemia and atherogenesis, suggestive of a latent submerged lipid metabolic defect consequent upon the removal of the pancreas. These results certainly did not take us very far along the road to a solution of the problem in man. Equally unsatisfactory were the negative results obtained in response to administering various pancreatic preparations to intact and depancreatized cholesterol-fed cockerels.

Since the one positive finding was a subtle defect in lipid metabolism in depancreatized cockerels, an attempt was made to elicit hidden abnormalities in carbohydrate metabolism and to render chicks diabetic. These objectives were achieved by glycocorticoid administration. With exhibition of whole adrenal cortical extract or hydrocortisone, definite evidence emerged of an abnormality in carbohydrate metabolism—i.e., of a relative insulin deficiency in depancreatized or alloxanized cockerels. In the intact birds, hydrocortisone induced a milder diabetes. Thus, chicks with steroid diabetes and with steroid-pancreatic diabetes were made available for atherosclerosis research.

When these cockerels with diabetes and hyperadrenocorticism were fed an atherogenic diet, they invariably developed inordinate hypercholesterolemia, owing to superimposition of hydrocortisone-induced hyperlipemia. Despite this more marked hypercholesterolemia, however, no significant intensification of atherogenesis was noted in either the aorta or the coronary

arteries. These results are generally in accord with the findings of others on cholesterol-induced atherogenesis in cortisone-treated steroid-diabetic rabbits. Nor are they irreconcilably in conflict with the observation that atherogenesis is markedly retarded in alloxan-diabetic rabbits (unless insulin is given, whereupon atherogenesis proceeds at control intensities). However, all these results in chicks and rabbits are apparently at variance with experiences with man, in whom both steroid and pancreatic diabetes almost invariably intensify atherogenesis (provided the minimal essential dietary prerequisites for atherogenesis are present over the life span).

Up to this point, we have considered "prophylactic-type" experiments only, i.e., experiments in which cholesterol feeding and alterations in endogenous function (pancreatectomy, corticoid or corticoid-pancreatic diabetes with hyperadrenocorticism) proceeded simultaneously. Such projects serve to answer the question, Is the given change in endocrine function an indifferent, intensifying or inhibitory (prophylactic) influence on cholesterol-induced atherogenesis? Equally valuable are "therapeutic-type" experiments, i.e., experiments in which atherosclerotic lesions are first induced by cholesterol feeding, and then allowed to regress over several weeks following cessation of the atherogenic diet, with alterations in endocrine function induced only during this latter period to assess their effect on regression of lesions.

Three such "therapeutic-type" experiments were undertaken to explore the diabetes problem further:

1. Induction of corticoid diabetes following cessation of cholesterol feeding retarded regression of both hypercholesterolemia and atherosclerosis.

2. Pancreatectomy also retarded regression of both hypercholesterolemia and atherogenesis, again indicating that removal of the pancreas induced concealed defects in lipid metabolism; the results of these two types of experiments were more consistent with findings in diabetic man.

3. Cockerels given insulin following cessation of cholesterol feeding exhibited a normal pattern of regression of hypercholesterolemia. No clear-cut effect of the hormone on regression of aorta lesions was noted. However, *regression of coronary lesions failed completely to occur in the insulin-treated cockerels.* Coronary atherosclerosis appeared to be aggravated in the insulin-treated birds, despite subsistence on plain mash for two weeks, resulting in a decline of plasma cholesterol to normal levels.

These findings with insulin were unexpected. Upon initial consideration, they appeared highly paradoxical. Would not one anticipate an antiatherosclerotic effect of insulin, the specific hormone for the correction of the metabolic defects in diabetes mellitus? The surprising finding of an opposite effect—of an atherosclerosis-perpetuating and intensifying action—compels us to ask a fundamental question: *Does administration of insulin to diabetics over the life span exert a significant atherogenesis-intensifying influence?* If so, why? We are now seeking the answer to this.

Estrogens in Experimental Atherosclerosis

By far the most striking results seen to date in studies on hormones and atherosclerosis have been those obtained with estrogens, while exploring the problem of the basis for the immunity of premenopausal women to coronary atherosclerosis. Given either parenterally or orally to cholesterol-fed cockerels, estrogens induced the following alterations: feminization; increase in the plasma $\frac{\text{free cholesterol}}{\text{total cholesterol}}$ ratio; enhanced hyperphospholipemia with lowering of plasma $\frac{\text{total cholesterol}}{\text{lipid phosphorus}}$ ratio to normal levels; depression of alpha lipoprotein levels; reduction of beta lipoproteins in the S_f 20–100 levels; prevention of coronary atherogenesis without influencing formation of aorta lesions. These effects were seen with all estrogenically active compounds (oral or parenteral, natural or synthetic) tested to date: α and β estradiol, mixed conjugated equine estrogens, estrone, equilenin, dienestrol, ethinyl estradiol, vallestril, diethylstilbestrol (pellet implantation). (This antiatherogenic effect of estrogen in the chick has recently been confirmed in a mammalian species, the rat.) On the other hand, several estrogen-like compounds of low feminizing potency failed to influence lipid patterns and coronary atherogenesis. Progesterone was likewise without influence. Estrogens retained their effectiveness against coronary atherogenesis in depancreatized chicks and in cockerels with hyperadrenocorticism and steroid diabetes. Moreover, estrogens prevented DCA- and cortisone-induced hypertension. The only method we have been able to find to prevent this antiatherogenic action of estrogen in the chick is by the simultaneous use of thiouracil.

Once these facts were established the question immediately arose, Can coronary lesions be prevented without feminization and/or alteration of plasma lipids? Appropriate experiments were designed to explore this problem. To date, partial success has been achieved. By combined administration of estrogens and androgen in a 1:3 ratio, it proved possible to maintain male secondary sex characteristics and yet induce the typical estrogen effects on the lipids and the coronary vessels of cholesterol-fed cockerels.

All the foregoing experiments explored the prophylactic potential of estrogens against cholesterol-induced coronary atherogenesis. The questions arose: What about the therapeutic potential of estrogens? Could coronary lesions, once established, be reversed? This problem was subject to experimental analysis. After a cholesterol-oil diet was fed for eight weeks, estrogen administration was instituted, with continued feeding of the atherogenic mash. At the end of 13 weeks, i.e., after five weeks of estradiol exhibition, coronary vessels were found to be practically free of lesions. The estrogen had reversed both the lipophage and fibroblastic

components of the coronary atherosclerotic plaques. Coronary atherosclerosis was again shown to be a reversible process!

All these studies were done in cockerels, i.e., the immature growing male chicks, utilizing dosages of exogenous estrogen that might be regarded as pharmacologic. Hence, further experiments were undertaken to determine the effects of the endogenous physiologic estrogen secretion of the egg-producing hen, and to compare the susceptibility of sexually mature male and female chickens to cholesterol-induced aorta and coronary atherogenesis. It was found that mature cholesterol-fed hens exhibited a plasma lipid pattern identical with that induced in cockerels by exogenous estrogens. Further, like estrogen-treated cockerels, they were remarkably immune to coronary (but not to aortic) atherosclerosis. In contrast, cholesterol-fed roosters (lacking a supply of estrogen) developed extensive lesions in both the coronary vessels and aorta. Thus, sexually mature chickens, unlike immature or castrated birds—but like sexually mature human beings—exhibited a significant sex differential in susceptibility to coronary atherogenesis. This antiatherogenic action of estrogens, confined as it was to the coronary vessels, again demonstrated that atherogenesis proceeds according to different laws in different arterial beds.

This immunity of estrogen-secreting, egg-producing hens to coronary atherogenesis was not due to mobilization and disposal of cholesterol and lipid via egg laying, since it was also present in oviduct-ligated hens, wherein yolks were deposited into the peritoneal cavity and subsequently reabsorbed. This freedom from coronary lesions is undoubtedly a consequence of the endogenous physiologic estrogen secretion of the egg-producing hen. This sex difference in susceptibility to coronary atherogenesis in mature chickens remarkably paralleled observations on human beings and thereby lent support to the concept that estrogens are decisively responsible for the relative immunity of premenopausal women to coronary disease.

Certainly considerable data are also available now from human studies suggesting that the physiologic estrogen secretion of the human female may exert a significant antiatherogenic influence. However, the last word on this still remains to be spoken. Nevertheless, the experimental and clinical findings were positive enough to encourage us to embark over two years ago upon a carefully controlled, thoroughgoing, long-term clinical study on the ability of estrogens to prevent recurrences of myocardial infarction and prolong life in males under 50 who had recently experienced a proved myocardial infarction. Preliminary results justify a guarded optimism. A definitive answer should be forthcoming in three to five years.

Conclusions

In conclusion, I can safely say that this program of experimental investigation on atherosclerosis has yielded results greatly reinforcing the

cholesterol-lipid-lipoprotein theory of atherogenesis. Further, it has demonstrated the profound influences of the hormones on lipid metabolism and the atherogenic process. Moreover—in confirmation of the basic thesis—it has indicated an intricate interplay between exogenous (diet) and endogenous (organism) factors, mediated via the humoral-hormonal-neural integrative mechanisms of the organism.

It is valid to conclude, therefore, that the concept of disease outlined in this report is apparently a sound one, above all because it has already rendered excellent service as a reliable theoretic guide to fruitful research on atherosclerosis. We are fully convinced of its rich promise for the future, provided there is the patience, perseverance and insight to pursue clues as they are unearthed.

Finally, it is worth noting explicitly that the recent upsurge of clinical and animal research on atherosclerosis has already yielded several new possible approaches to the care of human atherosclerotic patients and so may be of importance in the prevention of myocardial infarction. Extensive clinical investigation is still necessary to determine whether these approaches will eventually find a proved place in general therapeutics and prophylaxis. Such studies are proceeding, with promising but not yet definitive results. Regardless of the specific results with any given approach, the general pattern of attack on the over-all problem—proceeding within the context of the cholesterol-lipid-lipoprotein concept of atherogenesis—seems bound ultimately to produce a solution, including an effective approach to prophylaxis and therapy. Certainly, the progress of the last decade and the current activity in the field are a far cry from the hopeless, nihilistic attitudes towards this disease process which destructively dominated medicine until recently.

SUMMARIO IN INTERLINGUA

Atherosclerosis es un morbo que seque un alteration del metabolismo de cholesterol-lipido-lipoproteina.

Es presentate datos ab studios clinic e laboratorial que supporta le conception que dieta e hormones es de importantia fundamental in atherogenese coronari, le qual es le condition subjacente in plus que 95 pro cento de omne casos de infarcimento myocardiac. Le datos clinic es primarimente prendite ab studios epidemiologic del morbo. Es demonstrate que atherosclerosis es nunquam absente in un population que existe in omne stadios del vita super un dieta ric in calorias e in grassia de origine principalmente animal. Le contrario es ver pro populos con dietas povre in calorias e in grassia. Tamen, differentias individual non es explicabile per un simple concepto dietari de atherosclerosis, e etiam le differentia inter le sexos in lor susceptibilitate a morbo del arteria coronari non se explica super iste base. Nos conclude que hormones es de importantia primari in determinar iste differentias individual, providite que le "actionator" atherogenic in le forma de un dieta ric in calorias e in grassia es presente.

Nos presenta datos in supporto de iste theoria. Es discutite le influentia del pancreas e de insulina super atherogenese coronari. Es describite le capacitate de estrogenos a inhibir prophylacticamente e a reverter therapeuticamente le presentia de atherosclerosis coronari de origine experimental. Nos discute le signification que iste constatationes pote haber pro le therapia del morbo in humanos.

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PRESENT STATUS OF ANTICOAGULANT THERAPY IN THE TREATMENT OF MYOCARDIAL INFARCTION; THE USE AND MISUSE OF ANTICOAGULANTS; AN EVALUATION OF NEW ANTICOAGULANTS, THEIR INDICATIONS AND DOSAGE*

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THE use of anticoagulant therapy in the treatment of myocardial infarction is rapidly becoming accepted in medical centers and leading hospitals throughout the civilized world.[1] It is also being used well in many small communities where there exists the fortunate combination of a well trained, conscientious physician and a good laboratory capable of performing accurate prothrombin time tests.[2] While the report of the Committee on Anticoagulants of The American Heart Association constitutes the most comprehensive and detailed evaluation of this therapy, reports from more than 40 institutions confirming this study have appeared from the United States and foreign countries. In many of these, control cases have been studied which have not received anticoagulants. These studies have shown decreases in the death and thrombo-embolism rates comparable to those reported by the Committee on Anticoagulants. It is quite unlikely that these results could be duplicated purely by chance in areas as widely distributed as Chicago, Los Angeles, Minneapolis, Oslo, Stockholm, Paris, London, Edinburgh, Oxford, Vienna, Zurich, Lima, Santiago and New York, to mention only a few. The results of the Committee's studies were statistically significant in terms of improvement in death rate, and highly significant for reduction of many types of thrombo-embolic complications. The autopsy findings in these cases were even more convincing, since they were based on objective pathologic findings only.[3] From this large and worldwide experience it appears that this addition to our therapy is permanent.

A few critics have expressed skepticism regarding the value of anticoagulant therapy. For the most part, this has represented an expression of opinion indicating neither significant experience with anticoagulant drugs nor valid evidence to support their views.[4, 5, 6] Several authors[7, 8, 9] have reported small series of cases which have not confirmed the more universal experience. In several of these the authors themselves have pointed out inadequacies in the functioning of the laboratory or the clinicians during the study. It should also be understood that in this type of study, series

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smaller than 250 cases do not usually supply statistically valid material unless combined with other series.

The selection of patients with myocardial infarction for anticoagulant therapy has been a matter of some controversy. Russek and Zohman,[10] Schnur [11] and Baer et al.[12] have suggested that patients should be classified on the day of onset of the attack into mild or "good risk" cases, and severe or "poor risk" cases, and Russek has listed criteria which he feels may serve as a guide in determining "good risk" patients. These workers have claimed that the course and prognosis of the "good risk" patients thus selected on the first day are so free from risk that anticoagulant therapy should not be administered to them, at least unless some thrombo-embolic complication arises. They agree that anticoagulants should be administered to all severe or "poor risk" cases. This approach was regarded by many physicians as reasonable, and it certainly required less effort and expense, which added to its appeal. However, these conclusions were based on cases which were not matched against careful controls, and most of them were not diagnosed with the same type of criteria as those used by the Committee. In addition, the conclusions were usually based on death rates alone, which were indeed low in these cases, whereas little attention was paid to thrombo-embolic complications, which may nevertheless be serious or even permanently crippling. Even when criteria were applied to the cases in the series of the Committee which produced a selection in which the death rate was so low that little improvement was possible in the treated group, the thrombo-embolic complications showed a reduction of from 28 to nine per 100 cases, which was of some significance. Russek has claimed that the risk from anticoagulant therapy exceeds the risk of death in "good risk" cases. However, using the report of the Committee in support of this hypothesis, he has taken the total deaths associated with hemorrhage for the entire series, including the serious cases. This is not valid. Of 16 cases in whom hemorrhage was a factor contributing to death, only one was in the mild group. Serious hemorrhage is mostly seen in severe cases, as would be anticipated, since myocardial rupture and hemopericardium are among the leading factors.

Experience would lead us to believe that, even with the best of intent, no one can predict with certainty on the first day whether a patient will turn for the worse or for the better on the second day, or on any day thereafter. Levy,[13] Nichol [14] and many other experienced cardiologists have agreed with this position. In one series, in which an attempt was made to evaluate Russek's hypothesis, 29% of the patients had to be reclassified within the first 48 hours.[15] At the World Congress on Blood Coagulation, held in Basel, Switzerland, July 20 to 24, 1954, this question was considered by a panel of workers distinguished in this field. There was unanimous agreement among 11 members from eight countries that, unless contraindications exist, all patients should receive anticoagulant therapy;

and that attempting to withhold the treatment, unless there were some complications, was fraught with risk that, although it might be statistically small, was often too hazardous for the future of the individual patient.[1]

We are presently developing a survey to evaluate the current practice in clinics where important studies have been carried on with anticoagulants for myocardial infarction. In 20 of the 22 replies thus far received the investigators indicate that they have not found it wise to omit anticoagulant therapy based on the fact that the patient appears to be a "good risk" as of the first day. One group which has omitted anticoagulants in mild

TABLE 1

Cases of Mild Myocardial Infarction with Thromboembolic Complications

Patients	Myocardial Infarction	Treatment	Complications		Outcome
			Site	Days after Infarction	
1. F. P., 58, ♂	Posterior (mild)	None	Saddle embolus Gangrene right leg	7	Low thigh amputation
2. M. L., 56, ♂	Anterior (mild)	Bed rest Papaverine	Saddle embolus	30	Arterial insufficiency of legs
3. E. F., 46, ♂	Anterior (mild)	Bed rest	Saddle embolus Pulmonary infarct Gangrene both legs	9 86	Bilateral mid-thigh amputation. Death
4. M. S., 50, ♀	Anterior (mild)	Bed rest Dicumarol 2 wks. Discontinued 2 days PTA (P. T. 17")	Saddle embolus Gangrene left hallux	18	Self-amputation of left hallux
5. S. R., 69, ♂	Antero-septal (mild)	None	Right axillary occlusion Gangrene right hand ? CVA	45 60	Supracondylar amputation of right arm
6. A. P., 40, ♂	Anterior (mild)	Bed rest	Pulmonary infarct Renal infarct	6 20	Improved
7. M. P. M., 52 ♂	Posterior (mild)	Bed rest Dicumarol	Pulmonary infarct ? Saddle embolus (P.T. within normal range)	3–4	Arterial insufficiency of legs
8. R. M. M., 69 ♀	Anterior (mild)	Bed rest for 9 days	Pulmonary infarct	undetermined	Improved
9. S. F., 45, ♂	Anterior (mild)	None	Pulmonary infarct	undetermined	Improved
10. H. G., 58 ♂	Anterior (mild)	Bed rest	Pulmonary infarcts Saddle embolus	1–2 22	Improving

cases as a study has found that, while the death rate was as low as 1.8%, there were 10.5 definite thrombo-embolic complications per 100 cases, and four more probable complications.[16] That these thrombo-embolic complications may sometimes prove disastrous in so-called mild cases is illustrated by the cases which de Francisco, working with our group, has recently evaluated.[17] These patients, all mild and untreated or inadequately treated with anticoagulants, suffered the complications seen in table 1. In these 10 "good risk" cases it will be noted that there were thrombo-embolic episodes requiring one minor and four major amputations. Two patients were left with arterial insufficiency of the legs. Four recovered after serious

pulmonary emboli. There was one death. We do not believe that the risk of such complications should be considered lightly.

There are undoubtedly some patients in whom coronary occlusions occur in branches so minute and so located that the area of infarction never reaches the endocardial surface. In some such cases the patient is not aware of his occlusive episode. Others have only very mild transient discomfort, with borderline or no concomitant signs.

One reason for difference in experience and conclusions may rest in the fact that the Committee used only definite cases, with well established symptoms, signs and essential corroborative data. Patients with borderline diagnoses which might well actually represent other syndromes were not accepted in this study because it was felt that they might invalidate the findings. In such cases the physician's impression may be that of myocardial infarction, but this may be incorrect, and the true explanation of the mild disorder may never be known. Studies including such cases will show a lower death and complication rate.

The long-term therapy for the prevention or delay of subsequent myocardial infarctions or other thrombo-embolic complications was advocated in 1947 by Nichol and Fassett.[18] Though difficult to evaluate, increasing evidence presented by Lund,[19] Keyes et al.,[20] Suzman et al.,[21] Nichol and Borg,[22] Owren [23] and others, including our own group at Cornell,[24] suggests that patients who are kept on anticoagulants after one or two myocardial infarctions have a better outlook than those who are not. This parallels results with rheumatic heart disease with multiple embolization,[25, 26] cerebral thrombosis and embolism,[27, 28] and recurrent thrombophlebitis with or without pulmonary embolism. We have recently reported additional experience with long-term anticoagulant therapy in several groups of patients.[24] Two groups with myocardial infarction were included. In the first group 11 patients who had had two or more episodes of infarction were observed for 587 patient-months without anticoagulant therapy. During this time they experienced 49 thrombo-embolic episodes, 30 of which were myocardial infarctions, 10 were pulmonary emboli, two peripheral, two cerebral, four visceral emboli, and one episode of thrombophlebitis. In a total subsequent period of 393 patient-months (approximately two thirds as long) under anticoagulant therapy, these same patients suffered a total of only three thrombo-embolic episodes.

In a second group, 12 patients who had experienced single myocardial infarctions were treated for 554 patient-months, during which there was one questionable thrombo-embolic episode.

In the total myocardial infarction group eight patients have died. One of these was off anticoagulants for several weeks before death. A second showed no satisfactory explanation of his sudden death at autopsy. Two died suddenly, but unfortunately were not autopsied. Three died from congestive failure, and one with marked tachycardia, type undetermined.

More comprehensive studies must be carried out before the value of the long-term prophylactic use of anticoagulants after myocardial infarction is to be considered as conclusively established. At present, however, the trend appears rather strongly in that direction.

The correct use and the various indications for anticoagulant therapy have been outlined repeatedly. Our purpose has been to present the results which could be anticipated if a reasonably good technic was used under satisfactory conditions. Poor technic is no more to be condoned in this instance than in any other form of medical or surgical treatment. Indeed, here, because of the serious nature of the diseases and the type of action of the drugs involved, greater than usual care must be exercised. That anticoagulant drugs have been misused, sometimes with tragic results, no one can deny. This was to be expected. The technic and therapeutic approach required represented a departure from that with which most physicians were familiar, and the laboratory staff, often from the director to the technician, had to be impressed with the need of great care in the reporting of the prothrombin tests. This period of education took time, and unfortunately in some areas education in this regard must be continued for some time. The total number of deaths due to anticoagulant therapy is not known. The manner in which most of the figures have been compiled makes it seem likely that duplication has occurred. On the other hand, some deaths doubtless have never been reported. The major methods of misuse appear to be the following:

TABLE 2

Major Modes of Misuse of Anticoagulant Therapy

1. Self medication—without prothrombin tests for control
2. Prescribed medication without correct control
3. Anticoagulant therapy in the face of contraindications
4. Withholding anticoagulant therapy when indicated
5. Excessive dosage
6. Inadequate dosage

1. *Self-medication, Without Prothrombin Tests for Control:* Patients, nurses and even physicians have indulged in this dangerous practice and some deaths have resulted. It has been used to produce purpura and thus to avoid being drafted. It has been used by a patient with a profound psychoneurosis to produce a false disease state. This was effective in deceiving many physicians before the correct diagnosis was made.

2. *Medication Under a Physician's Instructions But Without Correct Control:* This occurred especially in the early period, when many physicians had not as yet appreciated the absolute need for prothrombin test control.

3. *The Administration of Anticoagulants in the Face of Definite Contraindications,* such as blood dyscrasias, bleeding peptic ulcers, recent brain surgery, and others which have been previously described. Inadequate laboratory service is a most important contraindication.

4. *The Withholding of Anticoagulant Therapy in the Presence of Definitive Indications for Its Use if Satisfactory Facilities Are Present for Its Administration:* Each physician must decide on the therapy for an individual case, and in this there may be a justification for a difference of opinion. However, the withholding of any valuable therapeutic agent in the face of indications for its use constitutes, in a sense, a misuse of that agent. We are constantly seeing patients from whom anticoagulants have been withheld until thrombo-embolic complications have developed. Some of these have been serious, as has been previously mentioned.

5. *Excessive Dosage:* This can occur inadvertently if the patient is very sensitive to the drug, unless the clinician is alert. It may occur if the clinician is not familiar with the correct dosage of the particular anticoagulant in use, or if the prothrombin time reported by the laboratory is inaccurate on the low side. It may occur if the patient is also taking large doses of salicylates, or certain antibiotics which disturb the flora of the intestinal tract.[29] This latter effect is believed to be due to interference with the production of vitamin K, which acts as a buffer against the action of the coumarin derivatives and phenylindandione compounds.

6. *Inadequate Dosage:* This may occur through caution in the face of some contraindications, and this is often justified. It has occurred when physicians have given "just a little anticoagulant" to avoid being criticized, but not enough to be of therapeutic value. This is, in a sense, more to protect the physician than the patient, and should be recognized as such. It has occurred when the laboratory has been inaccurate and has reported the times as too high. In our experience the optimal therapeutic zone is that which produces a prothrombin time ranging between one and one-half and two and one-half times the normal control, if that control is between 12 and 18 seconds. With control times of 15 seconds $\pm$ 1, an effort should be made to keep the prothrombin time between 25 and 37 seconds. There is, however, a definite but lesser therapeutic effect with a prothrombin time as low as 20 seconds.

There have been a few tragedies which resulted from bleeding from "silent," unrecognized ulcers or cancers of the gastrointestinal tract, or other conditions which should not be considered as due to lack of knowledge or care of the physician. This type of occurrence must be considered as a minimal calculated risk. From the beginning the leading workers in the field were able to demonstrate that serious hemorrhage could be reduced to a great rarity and could usually be well controlled. The introduction of vitamin K_1, which is practically as effective taken orally as parenterally, has added to the safety of this treatment. With increased experience the number of serious hemorrhages in proportion to the large numbers of patients receiving these drugs has been reduced to a level of relative insignificance. The price is eternal vigilance.

An Evaluation of Newer Anticoagulants

As predicted, following the recognition of the value of heparin and Dicumarol there has been great interest in the production of new anticoagulants, which may have advantages over existing ones. In 1948, before a meeting of this College, I listed the requirements for an ideal anticoagulant.[80] These were:

1. It should be therapeutically active when administered orally or parenterally, without producing digestive or hypersensitivity reactions.
2. Its action should be rapid, affecting the clotting tendencies of the blood within one hour.
3. The dosage should be easily standardized and fairly uniform for a given patient and as between different patients. The action should be predictable in terms of quantitative response.
4. It should be relatively nontoxic, with a wide safety zone between therapeutic effect and damage to important organs. It is obvious that there will always be some hazard from bleeding essential to the very nature of this therapeutic approach. This should not be regarded as a toxic effect but rather as an overextension of the therapeutic effect of the drug.
5. The action of the drug should be promptly terminated after stopping its administration or following the use of an effective antagonistic agent which, in itself, is free from undesirable effects.
6. A test for the activity of this substance should be sufficiently simple to permit its control by the family physician or, even better, by the patient.
7. The anticoagulant should be inexpensive.

Unfortunately, these criteria have not as yet been met by any single anticoagulant, but by using several in combination the rate of induction of activity can be brought about within a few minutes and maintained by oral administration thereafter. By the use of vitamin K_1 the cessation of activity can be achieved within three to six hours. Thus we have progressed, slowly to be sure, but definitely. The main difficulty still remains in the need for prothrombin tests for satisfactory control, and in the fact that these tests, even the bedside modifications, require training, careful preparation of the ingredients, and exactness in reading the end points.

Table 3

Coumarin Derivatives	Average Doses (Controlled by P.T.)		
	1st Dose	2nd Dose	Following
Dicumarol	300 mg.	100–200	25–100
Tromexan	1500	900	300–900
Cumopyran	150	75	50–75
Marcumar	21	9	3
Warfarin Sodium	50–75	25–37.50*	
Phenylindandione	150	50–75	25–75
Dipaxin	18	9	3–6

* Administered at 3 day intervals.

Following Dicumarol, other coumarin derivatives have been developed. *Tromexan* acts more rapidly than Dicumarol:[31, 32] 18 to 24 hours as against 48 to 72 hours, and when it is discontinued its activity ceases more rapidly: 12 to 30 hours in most cases, as against 48 to 96 or more hours. The dosage schedule for Tromexan and the other derivatives is noted in table 3. *Cumopyran* acts in about the same time as Dicumarol. Its action tends to be more prolonged, often requiring doses only once or twice a week.[33] *Marcumar* acts in 24 to 30 hours, between Dicumarol and Tromexan, and its action is prolonged. As with Cumopyran, its action may persist for seven to 10 days after cessation.[34] *Warfarin* and *Warfarin Sodium* (Coumadin Sodium) have also been recently introduced.[35, 36] Warfarin Sodium has the advantage of being available for intravenous use if the patient cannot take oral medication, or to speed up its action. Both of these substances may be used orally. Their action is more rapid than that of Dicumarol, and also more prolonged, often requiring only one or two doses a week. Additional coumarin derivatives are being studied and will be tested in the future.

In summary it can be stated that the newer coumarin compounds are metabolized and act at rates different from that of Dicumarol, but their fundamental actions in inhibiting prothrombin and factor VII are essentially the same. They also carry the same fundamental risk of producing bleeding if not properly controlled, not withstanding certain statements to the contrary. Their selection by the clinician must rest on what he wishes to accomplish in terms of rate of action and his familiarity with the tool he is to use. There is no evidence that the therapeutic effectiveness is dependent on the specific drug used, but only on the prothrombin and factor VII levels maintained.

Phenylindandione acts in much the same manner.[37] The speed of its action and cessation of action is similar to that of Tromexan. In our experience there have been a few more patients who have been resistant to its action than has been the case with the coumarin compounds, and a few skin rashes have been encountered. Otherwise, there is little difference. The same comments hold for *Dipaxin*,[38] a phenylindandione compound using a smaller dosage per kilogram of weight. These compounds involve the same risk as the coumarin compounds, namely, bleeding if the prothrombin time becomes too elevated or there is a bleeding tendency on the part of the patient. This is inevitable when the protective mechanism of thrombosis is interfered with.

The introduction of vitamin K_1, which is very active when taken orally, has greatly added to the safety of the use of all the above compounds. Ten to 50 mg. of vitamin K_1 in orange juice or on a piece of food will reduce the prothrombin time within three to six hours, and the duration of this action can be fairly well controlled according to the size of the dose. More than 50 mg. is rarely advisable. We have learned that larger doses, such as 250 mg., which were given at first, are undesirable since, while they act

slightly or no more rapidly, they render the patient resistant to a renewal of his anticoagulant therapy, which may be highly desirable.

Table 4 is presented to emphasize that, of the anticoagulants with heparin-like action, *heparin* remains the only one which is satisfactory for use in humans. The indications and directions for the administration of heparin have been reported many times and are so well known to this audience that I will not discuss them. *Paritol* [39] and *Treburon* [40] have been tried clinically and both have produced reactions of shock, urticaria and alopecia with sufficient frequency to force their abandonment. *Phosphorylated hesperidin,* first recognized by Sheppard [41, 42, 43] to be an anticoagulant with heparin-like properties, is still in the experimental stage. It differs from heparin in that the body apparently provides no cofactor similar to that which greatly enhances the effectiveness of heparin when used clinically.

In another category of so-called anticoagulants, *trypsin* has been advocated for intravenous use in doses as great as 250 mg.[44] Taylor, working with us, has confirmed the work of Tagnon [45, 46, 47] and others, who established the fact that such doses have potential danger. Trypsin first pro-

TABLE 4

Heparin	50–75	Every 4 hours, or crystalline 100 B.I.D.
Paritol	x	
Treburon	x	
Phosphorylated Hesperidin	x	
Trypsin I.V.	x	
I.M.	x	
Plasmin	x	

duces a phase of increased clotting tendency, then in large dosage a phase of incoagulability. Clots were produced in the right side of the heart and many veins in the bodies of rabbits. Kellner [47] demonstrated focal necrosis in the heart muscle, and Lieberman [48] has demonstrated adverse electrocardiographic changes with equivalent dosage in animals. In man it was found that many veins thrombosed at the site of injection, a curious reaction for an allegedly useful anticoagulant, and at least three patients have died with widespread thrombosis following such dosage of trypsin. Recently the recommendations by the advocates of this substance have dropped from 250 mg. intravenously to 2.5 mg. subcutaneously or intramuscularly. We have been unable to measure any effect whatever on the clotting mechanism with such dosage. It is now claimed that the important action is anti-inflammatory, and that this produces resolution of the inflammation of phlebitis.[49] Since these observations have been based largely on superficial thrombophlebitis, they are very difficult to evaluate because in most cases this subsides in a few days with rest and conservative treatment and, if necessary, can almost always be checked by the coumarin derivatives. Injections of

trypsin have frequently resulted in local inflammation or necrosis. It cannot be recommended as a sound therapeutic agent at this time.

Another anticoagulant with an enzymatic action under study at present is *plasmin*.[50, 51, 52] It apparently does exert a favorable effect toward the disintegration of fresh thrombi, but it is still in the experimental phase and its evaluation for clinical use is only now being undertaken.

Summary

The use of anticoagulants in the treatment of myocardial infarction is now being adopted in many leading centers throughout the civilized world. It is also being used in many smaller communities with suitable facilities. Some workers believe that anticoagulants should be used only for severe cases, or for those who have already suffered thromboembolic complications; but the trend in the leading clinics with large experience with this form of therapy is in favor of using anticoagulants in all cases of myocardial infarction unless there are contraindications to their use.

Long-term anticoagulant therapy after one or more myocardial infarctions appears to give the patient a better prognosis. However, further study and analysis are essential before this position can be accepted as absolutely conclusive.

Major factors responsible for the misuse of anticoagulants include:

1. Self-medication without prothrombin tests.
2. Medication under physician's directions but without correct control.
3. Administration of anticoagulants in the face of contraindications.
4. Withholding of anticoagulant therapy in the presence of definite indications.
5. Excessive dosage.
6. Inadequate dosage.

Accumulated experience with these drugs has reduced the relative incidence of serious hemorrhage. Serious hemorrhage is rare in mild and moderately ill patients. The availability of vitamin K_1 has increased the safety.

New coumarin and phenylindandione derivatives have been introduced for clinical use, and these have been discussed. Their rate and duration of action vary, but their effectiveness depends fundamentally on their action on prothrombin and factor VII activity. The value of these drugs does not appear to be very different, and the facility with which the physician uses them probably constitutes the most important single factor in securing therapeutic results with safety.

Heparin remains the only drug of its type suitable for clinical use.

The so-called anticoagulants with enzymatic properties are thus far in an experimental phase and are not recommended for general use in man, pending much more comprehensive and critical evaluation.

Summario in Interlingua

Le uso de anticoagulantes in le tractamento de infarcimento myocardiac es practicate de plus in plus a multe prominente centros in omne partes del mundo civilisate. Illo es etiam practicate in numerose minus grande communitates que possede le requirite facilitates. Alicun laboratores crede que anticoagulantes deberea usar se solmente in sever casos o in casos que ha jam disveloppate thrombo-embolic complicationes. Sed le tendentia general in le major clinicas con extense experientias in iste forma de therapia favora le uso de anticoagulantes in omne casos de infarcimento myocardiac in que illo non es contra-indicate per altere factores.

Therapia anticoagulante a longe durantia in patientes qui ha habite un o plure infarcimentos pare meliorar le prognose. Nonobstante, studios additional e analyses plus detaliate es necessarie ante que iste position pote esser acceptate como absolutemente conclusive.

Le factores responsabile pro le abuso de anticoagulantes es numerose. Illos include le sequente.

1. Auto-medication del patiente sin test de prothrombina.
2. Medication sub le direction de un medico sed sin correcte regulation.
3. Administration de anticoagulantes in despecto del presentia de contra-indicationes.
5. Doses excessive.
6. Doses inadequate.

Experientias cumulative con iste drogas ha reducite le frequentia relative de serie hemorrhagias. In leve e moderatemente sever casos le occurrentia de serie hemorrhagias es rar. Le disponibilitate de vitamina K_1 ha contribuite al reduction del risco.

Nove derivatos de coumarina e de phenylindanediona has essite introducite in uso clinic. Le intensitate e duration de lor action varia, sed ultimemente lor efficacia depende de lor influentia super le activitate de prothrombina e del factor VII. Il pare que le valor de iste varie drogas non differe grandemente, e le facilitate in lor uso disveloppate per le medico individual es probabilemente le plus importante factor in lor non-riscose functionamento.

Heparina remane le sol droga de su genere que es recommendabile pro usos clinic.

Le si-appellate anticoagulantes con qualitates enzymatic se trova ancora in un phase experimental. Lor uso in humanos es non a recommendar ante le completion de un plus comprehensive e critic evalutation.

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THE CONTROL OF EXCESSIVE EFFECT BY ANTICOAGULANTS * †

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Introduction

The decision to administer anticoagulant drugs should imply familiarity with the indisputable complication of hemorrhage which they evoke. This report is concerned with factors which are important in the control of excessive effect by these potent drugs.

Available Anticoagulants and Important Pharmacologic Properties

A few years ago selection of an anticoagulant was not a problem, for the choice was limited to Dicumarol or heparin. In the search for more satisfactory preparations several derivatives have become available, and their number is now sufficiently large to be confusing. Pertinent summaries are to be found elsewhere [1-5] regarding the details of administration and special features of the drugs with anticoagulant effect now available. In general, they may be classified (table 1) on the basis of their resemblance to Dicumarol or to heparin. The problem of excessive effect is associated to some extent with variable pharmacologic properties. With respect to the selection of an anticoagulant, the clinician may well consider these questions: How potent is this drug in comparison with Dicumarol? Does a single dose produce a transient or a sustained effect? Does this drug possess an appreciable cumulative effect? After the last dose, what is the time interval required for the clotting mechanism to revert to a level at which the hazard of bleeding is largely diminished?

None of the available preparations possesses all of the properties of the perfect anticoagulant; moreover, all are capable of provoking hemorrhage. Their use therefore implies a program of watchfulness. If one administers them to a sufficient number of patients the problem of bleeding will eventually be encountered in spite of one's best efforts to avoid it. Bleeding, then, is

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an accepted and calculated risk; its frequency and hazard, however, may be minimized by attention to certain precautions in the use of these potent therapeutic agents.

Measurement of the Effect of Coumarin and Indandione Derivatives Upon the Clotting Mechanism

Coumarin and indandione derivatives are peculiarly devoid of known pharmacologic action with the exception of their unique effect upon the blood clotting mechanism. After oral or intravenous (Coumadin and Marcumar) administration, this is demonstrated by prolongation of the plasma clotting time as determined by specialized tests. This is commonly said to be achieved through their effect upon "prothrombin." Recent studies indicate that these drugs may alter still other factors in the clotting mechan-

Table 1

Available Anticoagulants

For Oral Administration

Coumarins

Dicumarol	Tromexan
Cumopyran	Coumadin
Marcumar*	Sintrom (G-23350)*

Indandiones

Hedulin or Indon
Dipaxin*

For Intavenous Administration

Heparin

heparinoid Dextran sulfate*

Coumarins

Coumadin
Marcumar*

* For clinical investigation only, April, 1955.

ism. Thus, Dicumarol, Tromexan and phenylindandione [6, 7, 8] diminish proconvertin (Factor VII) simultaneously with and sometimes to a greater extent than prothrombin. The effect of Dicumarol upon proaccelerin (Factor V) is not clear; more recent work [9] suggests that possibly another factor in the clotting mechanism may be involved when Dicumarol is administered. Other possibilities among the effects of Dicumarol have been suggested by Seegers.[10]

The classic theory (Morawitz) postulates two steps in the clotting of blood:

$$1\text{—Prothrombin} + Ca^{++} + \text{Thromboplastin} = \text{Thrombin}$$
$$2\text{—Fibrinogen} + \text{Thrombin} = \text{Fibrin}$$

The specialized tests for plasma clotting time determinations used to guide administration of anticoagulants are known as one-stage tests if no attempt

is made to separate the two steps in coagulation (Quick one-stage prothrombin test, Owren P & P Method, Ware Modification of the Owren Method, and the "bedside" method of Ziffren et al.[14]). By contrast, in the two-stage method of prothrombin determination (Warner, Brinkhous and Smith, and Ware and Seegers modification), allowance is made for the conversion of prothrombin to thrombin, following which the second stage of the clotting process is allowed to proceed.

Measurement of Prothrombin Activity by the Quick Method

In Quick's one-stage method,[13] "prothrombin" determination is made by adding thromboplastin reagent and calcium chloride to oxalated plasma and timing the formation of the clot. When the calcium concentration is optimal, when temperature is constant, when thromboplastin is added in excess, Quick postulates that prothrombin is made the limiting factor and therefore the determiner of the clotting time. Since the concentration of

Table 2

Expressions of Prothrombin Activity Based on Quick Method

(A) As % normal prothrombin concentration
derived from standard dilution curve
Goal: 20% (33 sec.) to 30% (22 sec.)

(B) As % normal prothrombin
Derived from: $\frac{\text{control (sec.)}}{\text{patient (sec.)}} \times 100$

Goal: 30 to 50%

(C) As seconds of prothrombin time
Goal: 2 × control (24 to 28 seconds)
not in excess of 35 seconds

thrombin is determined by the speed of coagulation, the clotting time (or "prothrombin time") becomes the measure of the prothrombin level of the blood. With the exception of thromboplastin, all of the coagulation factors, including the labile factor (Factor V, or proaccelerin), are present in proportions actually occurring in the patient's blood. By this method normal oxalated human plasma yields a "prothrombin time" of 12 seconds, which is assumed to be equivalent to 100% "prothrombin concentration." The Quick one-stage prothrombin test is a moderately simple procedure, being especially practical for clinical laboratories. Standardization is essential. When it is performed correctly, many clinicians are agreed that the procedure can be relied upon as a reasonably safe and accurate guide to dosage of the coumarin and indandione derivatives.

On the basis of this procedure, information of prothrombin activity can be reported to the clinicians in one of three expressions (table 2). To express the prothrombin activity of the patient's blood in terms of normal concentration, the laboratory must construct a dilution curve whereby pro-

thrombin time can be related to prothrombin concentration. From this familiar hyperbolic curve prothrombin activity may, for example, be reported as: "Control, 12 sec.; patient's prothrombin time, 24 sec., or 20% of normal concentration." The therapeutic range, in terms of prothrombin concentration, is usually defined as lying between 10 to 30% of normal.

Some clinicians [11, 12, 42] have chosen to express prothrombin activity in terms of the ratio derived from the formula:

$$\frac{\text{prothrombin time of control}}{\text{prothrombin time of patient}} \times 100.$$

If these values were, respectively,

$$\frac{12 \text{ seconds}}{24 \text{ seconds}} \times 100,$$

the ratio would become 50% of normal. Experience has demonstrated that this therapeutic goal ranges from 30 to 50%. The "prothrombin index" derived in this manner, because it, too, is expressed in per cent, is easily confused with "per cent prothrombin concentration"; these values are not interchangeable; confusion, in this respect, may be dangerous.

To eliminate confusion in expression of "prothrombin" activity, it has been suggested [25] that only seconds of prothrombin time be reported to the clinician. Upon this basis, Dicumarol is administered until the patient's prothrombin time exceeds the control value by two times (e.g., until the patient's prothrombin time is 24 seconds in comparison to the control value of 12 seconds); it is not allowed to exceed 35 to 40 seconds. This recommendation is based on the fact that with a well standardized dilution curve a prothrombin value of twice the control, or 24 seconds, corresponds to a prothrombin concentration of approximately 20%, while a value of 35 seconds corresponds to a prothrombin concentration of about 10% of normal.

Practice has proved that any one of these three methods of expressing prothrombin activity is satisfactory as long as they are not confused and are based on carefully performed prothrombin times by the Quick procedure. To use them safely and effectively it is suggested that the clinician inform himself with regard to the test performed by his laboratory to measure prothrombin and the expression of prothrombin activity employed. It is the responsibility of the laboratory to report to the clinician the value of the control and patient's prothrombin time in seconds. Reasonable daily consistent control values are essential; if, in addition, prothrombin is expressed as per cent, the mode of derivation of this figure should be clearly indicated.

To increase sensitivity of the Quick procedure Link et al.[16] made the modification of plasma dilution (12.5%). Shapiro [16] recommends determination of the prothrombin time of whole and dilute plasma to reveal the relative activity of coagulation inhibitors and accelerators: the results are reported in seconds.

The Owren One-Stage P and P Method

Investigations of recent years have made it evident that the phenomena of blood coagulation are much too complex to allow expression by the simple classic formula referred to earlier. In particular, it has become evident that there are other variables in the clotting mechanism which are important. Pertinent to this discussion, it is evident that, in addition to thromboplastin, there are accessory factors required for the conversion of prothrombin to thrombin. According to Owren,[6, 7, 8] proconvertin (Factor VII) is the plasma factor necessary for this conversion. Proaccelerin (Factor V), or the plasma Ac-globulin of Seegers, is an additional factor also taking part in the conversion of prothrombin to thrombin. How prothrombin interacts with one or more of the converting factors is not known.

Owren has emphasized that the Quick prothrombin time measures the time needed for the thrombin titer to reach the clotting level in the presence of a fixed amount of thromboplastin and calcium. He stresses that, as such, it is not a specific measure of prothrombin concentration but varies with the absolute as well as the relative concentration of prothrombin, proconvertin and proaccelerin. He further stresses that the Quick test, done on whole plasma, is insensitive, since significant prolongation of the clotting time does not appear until the concentration of prothrombin, proconvertin or proaccelerin is reduced below 50% of normal. In addition, in the Quick procedure, various anticoagulation factors (antithrombin, antithromboplastin and heparin) are uncontrolled.[17]

Owren [6] has devised a one-stage method for measuring the effect of anticoagulants upon the clotting mechanism which, in his experience, is free of the defects of the one-stage test of Quick. By this method (prothrombin and proconvertin), quantitative determination is made of the combined effect on blood clotting by the simultaneous reduction of prothrombin and proconvertin. By the use of special filtered ox-plasma (prothrombin free), a constant and excess source of fibrinogen and proaccelerin is provided. To obtain increased sensitivity, the plasma to be tested is diluted tenfold by veronal buffer; the procedure is further distinguished by the use of frozen human brain thromboplastin.

Owren is of the opinion that by this method a more specific expression of the effect of Dicumarol is obtained, because Dicumarol therapy decreases both prothrombin and proconvertin. Proconvertin is sometimes decreased to a lower level than is prothrombin, so that in the hemorrhagic state, although prothrombin may still be in the optimal therapeutic range, proconvertin may have almost disappeared. The determination of the combined effect (P and P method) is just as reliable, in Owren's opinion, as is the specific determination of both prothrombin and proconvertin. For application to anticoagulant therapy, construction of a dilution curve is recommended for a standard of reference. Search of available publications has not disclosed an illustrative curve, nor have data been found with reference

to the crucial points on the curve. The optimal therapeutic range of hypocoagulability by the P and P method in Owren's hands lies between 10 to 30%; hemorrhagic complications caused by anticoagulants have not been observed with P and P values above 10%. Relapses of thrombotic episodes, on the other hand, have been very rare when the P and P value has beer kept below 30%.

Lehmann [18] has emphasized with regard to the Owren procedure that because of the basic instability of ox-plasma, normal plasma and patient plasma, changes from the initial values occur which impair the validity of the specimen used for standardization of the procedure and calculation of per cent values. "The per cent values as representative for the real state of prothrombin and proconvertin in the blood are therefore a delusion. The index values have certain advantages; prothrombin times are more adequate—both when corrected to a standard coagulation curve are directly proportional to the bleeding danger." Owren's P and P method is not a simple test to perform. Complete compliance with the published directions involves preparation of thromboplastin from human brain and special filtered ox-plasma from blood obtained at the slaughterhouse.

The Ware Modification of the Owren One-Stage Prothrombin Test

By certain modifications, Ware and Stragnell [19] made the Owren P and P method more convenient for the average clinical laboratory to perform. In part, these include the use of dried thromboplastin and a preparation of prothrombin-free beef plasma, both of which may be obtained from commercial sources. Dried human plasma, utilized as a source of prothrombin for construction of a reference standard (100% and 20% plotted on log log paper), is especially helpful since it provides, from day to day, an easily accessible and reproducible reference. Prothrombin activity of the test plasma is stabilized by drawing the blood into an anticoagulant solution modified by the addition of heparin. As in Owren's procedure, an excess of proaccelerin is provided through the use of beef plasma; a 1:10 dilution is also made of the test plasma.

By this method, reasonable constancy in the range of prothrombin levels in normal individuals may be expected. Ware and Stragnell reported that the majority agree within a range of plus or minus 15%. The 100% prothrombin standard gives a prothrombin time between 23 and 33 seconds; the 20% standard may vary from 40 to 60 seconds. At levels of 10% prothrombin or below, the clotting times may not relate well to prothrombin concentration. Our experience confirms these values and the advantage claimed for the procedure, namely, ease of standardization and reproducibility, which are facilitated by commercially available test plasma and reagents. Since the test is carried out on dilute plasma, one might expect reduction of the intensity of effect of circulating heparin upon the clotting

time. The report that the presence of circulating heparin in blood does not significantly alter the response of the test plasma to measurement of prothrombin by this method is substantiated in our limited experience (table 3).

The Two-Stage Procedure for the Measurement of Prothrombin

In the two-stage method of prothrombin determination, as described originally by Warner, Brinkhous and Smith,[20] the entire conversion of prothrombin to thrombin is allowed to proceed, following which the second reaction, e.g., the changing of fibrinogen to fibrin through the influence of thrombin, is utilized to measure the amount of thrombin formed. It was later appreciated that proaccelerin (Factor V or plasma accelerator globulin)

Table 3

Effect of Intravenous Heparin upon Blood Clotting Tests
F. F. 45 year old man. "Normal"

Time Baseline	Clotting Tests		
	Lee-White Min. 12'30"	Quick Sec. 12.5 (100%)	Modified Owren (Ware) Sec. 23.2 ("100%")
	100 mg. heparin sodium (Upjohn) injected I.V.		
90 sec.	6 hrs. no clot	12.5	24.2
11 min.	6 hrs. no clot	180+	26.3
30 min.	3 hrs. 30"	37.2	26.2
1 hour	3 hrs. 23"	39.3	24.1
2 hours	2 hrs. 34"	22.8	24.0
3 hours	1 hr. 30"	17.4	22.0
4 hours	42 min.	14.2	23.2
6 hours	22 min.	12.5	26.2

The effect of 100 mg. of intravenous heparin upon the clotting mechanism is reflected by rapid increase in the Lee and White clotting time and the Quick one-stage prothrombin time. In contrast, the prothrombin activity, measured by the modified Owren (Ware) procedure, is not appreciably influenced by the presence of large amounts of circulating heparin.

affects the rate of formation and yield of thrombin. Ware and Seegers [21] modified the method by supplying an adequate amount of accelerator globulin (diluted bovine serum), on the basis of which they believe the two-stage method specifically and accurately measures prothrombin. In this method activity of antithrombin and antithromboplastin is reduced by dilution of the plasma; the problem of variations in fibrinogen is eliminated by addition of a standardized fibrinogen solution, and the conversion rate of prothrombin is not an important factor. Normal human plasma is found to contain about 300 units of prothrombin.

Olwin [17, 22] has compared the results of the one-stage (Quick) procedure on whole plasma with the two-stage method, with or without added accelerator globulin and plasma diluted to 12.5% (Link). The one-stage

method in some instances gave results parallel to and usually higher than those of the two-stage test. In the first week of therapy, however, the relationship between the one-stage and the modified two-stage tests might be reversed; that is, the one-stage test might give a lower figure than the two-stage. Hurn, Barker and Mann [23] observed that early in the dicumarolization of patients the one-stage method (Quick) always showed a lower figure than did the two-stage.

Olwin concluded that if the two-stage reading was below 10% of normal and the one-stage was above 10% of normal, bleeding was unlikely; when both methods were below 10%, bleeding might be imminent. He has more recently [22] reported that, whereas the two-stage test is a more accurate measure of available prothrombin, the one-stage test as the measure of the activity of a number of factors, both coagulation and anticoagulation, is a more accurate gauge of the likelihood of bleeding. In Dicumarol therapy, however, where efforts are directed toward control of prothrombin, the two-stage method is the one of choice. The one-stage test, however, is conceded to be of value as a measure of the safety factor.

TABLE 4

Critical Level of Hypoprothrombinemia in Anticoagulant Therapy

	Therapeutic	Prophylactic
By Quick one-stage		
Allen et al.	10 to 30%	
Wright et al.	11 to 23%	25 to 38%
Brambel		40 to 50%
By Owren P & P method		
Owren	10 to 30%	10 to 30%
By modified Owren (Ware)		
Griffith	10 to 20%	10 to 30%
By modified two-stage		
Olwin	20 to 30%	

CRITICAL LEVEL OF HYPOPROTHROMBINEMIA TO BE ACHIEVED WITH ANTICOAGULANTS

Agreement is lacking with regard to the critical level of hypoprothrombinemia to be obtained with anticoagulant drugs. The various ranges of prothrombin levels advocated by several specialists are presented in table 4. Allen and others,[24] on the basis of six years' experience with Dicumarol in 2,307 cases, stated in 1947: ". . . We have attempted to maintain the values for prothrombin (Quick) in the blood between 10% and 30%, since our experiences have indicated that significant hemorrhage seldom occurs when the value for prothrombin in the blood is more than 10%, and that intravascular thrombosis seldom occurs when the value for prothrombin is less than 30%. It is possible that Dicumarol may be administered with satisfactory results if the value for prothrombin in the blood is not reduced as

much as we have indicated." According to the technic used at the Mayo Clinic, the value of 10% corresponded to 58 seconds and the value of 30% to 27 seconds. Wright et al.[25] have chosen a therapeutic range, also based on the Quick method, which varies from 11 to 23%. Brambel [26] has noted that protection appears to be offered when coumarin anticoagulants are used prophylactically if the prothrombin level (Quick) is maintained at 40 to 50%.

Olwin has stated that with the modified two-stage procedure the ideal therapeutic range is 20 to 30%. Griffith and others,[27] using the Owren one-stage test as modified by Ware, have studied the critical level of hypoprothrombinemia necessary for satisfactory prophylaxis of patients in con-

TABLE 5

Correlation of Prothrombin Activity by Two-Stage and One-Stage Tests in Patients Receiving Oral Anticoagulants

With Quick Prothrombin Concentration in Range of:	Two-Stage*	Owren % Prothrombin	Modified Owren (Ware) % Prothrombin
10 to 30%	19% to 47% (70 to 170 units)	<10% to 10%	<10%
30 to 40%	22% to 63% (80 to 234 units)	<10% to 16%	<10% to 14%
40 to 50%	30% to 100% (103 to 360 units)	12 to 25%	10 to 20%
50 to 60%	50% to 100% (184 to 360 units)	20 to 38%	12 to 30%

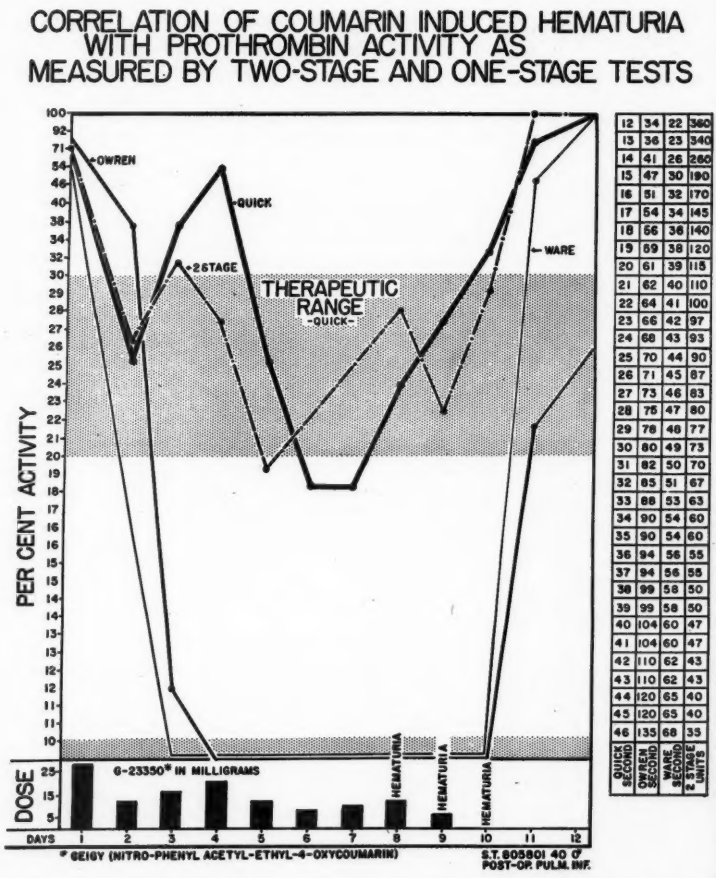
* Ware-Seegers modification.

The therapeutic levels of prothrombin activity, based on various methods of measurement carried out simultaneously, are not necessarily comparable. There is fairly good correlation of prothrombin activity as measured by the Quick one-stage and the two-stage procedure when the Quick prothrombin concentration is in the 10 to 30% range. The corresponding levels for the other one-stage stage tests are, however, definitely below the recommended safe levels. When the therapeutic range which Owren and Ware advocate (10 to 30%) is achieved, the corresponding values by the Quick procedure are in the range generally conceded to be nontherapeutic.

gestive failure treated by anticoagulants. Reduction of prothrombin levels to less than 60% was associated with a striking reduction in incidence of thrombo-emboli: ". . . The upper limit of safety for prophylactic anticoagulant therapy may be approximately 45%. . . . When active intravascular clotting has begun, it is probably necessary to depress the prothrombin level to 10 to 20% of normal." Owren's therapeutic goal lies in the range of 10 to 30%.

Alexander [28] has recently stated: "There can no longer be any question that under experimental conditions, intravascular coagulation can be blocked or hindered by anticoagulants. Thus the rationale of their therapeutic use is sound." With regard to definition of the "effective" drug dose or the

"best" level at which prothrombic activity should be kept for effective but safe therapy, he commented: "There is at present no unequivocal answer to these questions. I do know, however, that when the one-stage prothrombic activity (Quick) is reduced below 10% of normal, thrombin formation is markedly slowed and reduced. In my opinion, furthermore, a level of 5 to 10% of normal is reasonably safe, if all other hemostasis functions are normal. When the prothrombic activity drops below this value, hemorrhage is likely to ensue."



QUICK SECOND	OWREN SECOND	WARE SECOND	2 STAGE UNITS
12	34	22	360
13	36	23	340
14	41	26	260
15	47	30	190
16	51	32	170
17	54	34	145
18	56	36	140
19	59	38	120
20	61	39	115
21	62	40	110
22	64	41	100
23	66	42	97
24	68	43	93
25	70	44	90
26	71	45	87
27	73	46	83
28	75	47	80
29	78	48	77
30	80	49	73
31	82	50	70
32	85	51	67
33	88	53	63
34	90	54	60
35	90	54	60
36	94	56	55
37	94	56	55
38	99	58	50
39	99	58	50
40	104	60	47
41	104	60	47
42	110	62	43
43	110	62	43
44	120	65	40
45	120	65	40
46	135	68	35

FIG. 1. Prothrombin activity, as simultaneously measured by four different procedures, is not necessarily comparable. In this patient the prothrombin level as measured by the Owren and Ware methods quickly fell and remained below the therapeutic range (based on the Quick procedure), although the Quick and two-stage values were within that range. Gross hematuria developed on the eighth day of treatment; vitamin K was not administered.

The Quick one-stage procedure has been employed to guide the dosage of the coumarin and indandione drugs in patients at the University of Michigan Hospital over a period of nine years. We have adopted the therapeutic goal as defined by Allen et al.,[19] expressing prothrombin activity in terms of per cent of normal concentration. Our experience parallels that

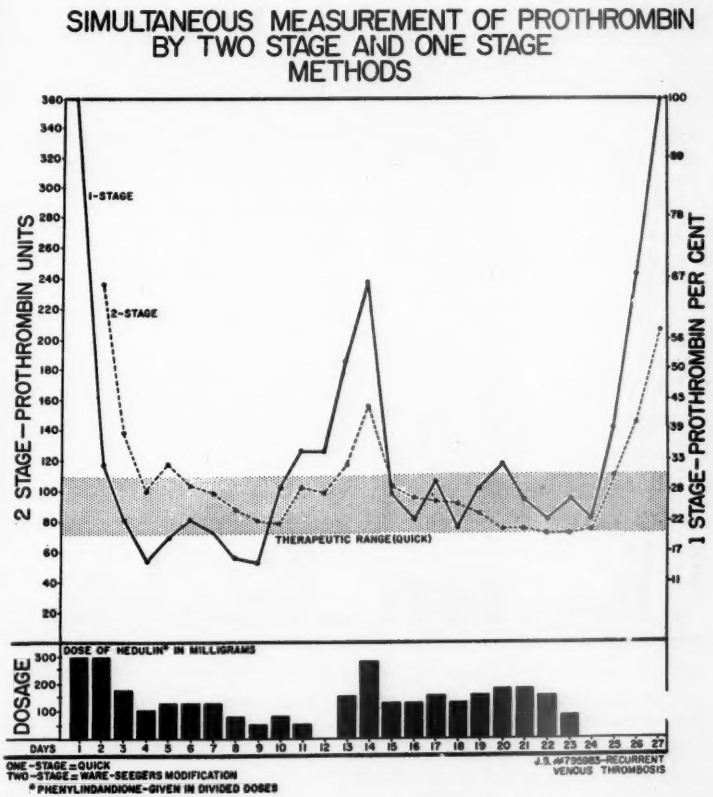


FIG. 2. Prothrombin activity when measured by the Quick one-stage and the two-stage methods (Ware-Seegers modification) is found to correlate fairly closely. In the first week of therapy the one-stage test gave a lower figure than did the two-stage test; thereafter, the relationship tended to be reversed.

of many other clinics, e.g., for routine clinical use, the procedure has been quite satisfactory. Our incidence of bleeding, however, has ranged from 5 to 10%. In an attempt to lessen this hazard, we have set up control studies in which the prothrombin levels of patients to whom anticoagulants are being administered, as described above, are also checked simultaneously

by determinations after the methods of Owren and Ware, and the two-stage modification of Ware and Seegers.

This experience has drawn our attention to a fact recently pointed out by Smith et al.[29] but not generally appreciated. The therapeutic levels (table 4) as advocated by proponents of the various methods of prothrombin testing are not necessarily comparable. In table 5 comparison is shown of the per cent prothrombin level, recorded by the Quick procedure, as contrasted by simultaneous readings obtained by the one-stage methods of Owren and Ware, and the two-stage procedure. It is seen that when the prothrombin level by the Quick method is in the therapeutic range of 10 to

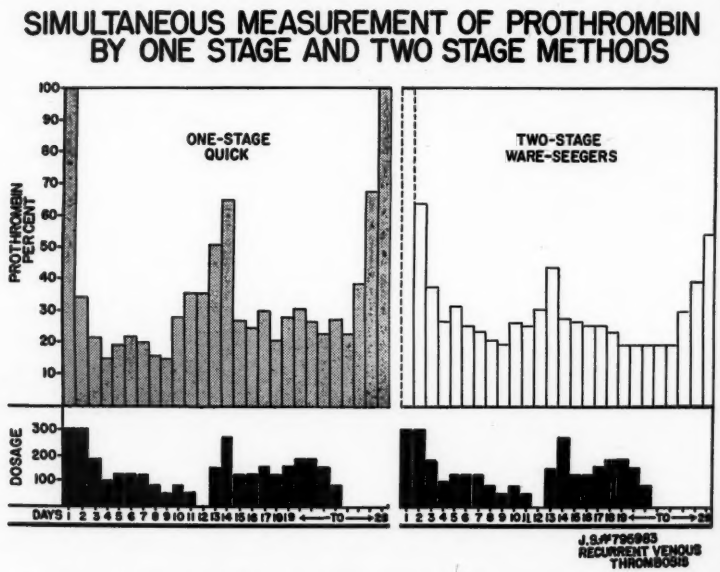


FIG. 3. Prothrombin activity when measured by the Quick one-stage and the two-stage methods (Ware-Seegers modification) is found to correlate fairly closely. In the first week of therapy the one-stage test gave a lower figure than did the two-stage test; thereafter, the relationship tended to be reversed.

30%, the corresponding values for the other one-stage tests are definitely below the recommended safe levels. On the other hand, when the therapeutic range which Owren and Ware advocate is achieved, the corresponding values by the Quick method tend to be in the range of 40 to 50% of normal. (This range is generally considered nontherapeutic.) In contrast, there was fairly good correlation between the Quick and the two-stage methods. Further graphic illustration of these facts, in an individual patient, is illustrated in figure 1, where it is seen that by the Owren and Ware methods the level of prothrombin quickly fell below the therapeutic range,

although the Quick and two-stage values were within that range. The case was of further interest in that the gross hematuria developed on the eighth day of treatment; with cessation of the drug, there was a prompt return of all values to normal; vitamin K was not administered. Figures 2 and 3 illustrate, in another patient, the similarity of prothrombin activity when measured by the Quick and the two-stage methods.

General Precautions in the Use of Coumarin and Indandione Drugs

In addition to awareness of the methods used to determine therapeutic levels of anticoagulants, proper selection of patients helps to prevent excessive effect. Contraindications (table 6) to anticoagulant therapy do exist and must be borne in mind if the pitfall of hemorrhage is to be avoided. It is desirable to obtain a baseline prothrombin value before anticoagulants are administered. In most instances this may be drawn at the time treatment is initiated. If this happens to be in the middle of the night, the blood may

Table 6

Contraindications to Be Observed in Anticoagulant Therapy

1. Lack of experience and reliable daily prothrombin estimations.
2. Hypoprothrombinemia (jaundice, biliary fistula, liver damage).
3. Recent surgical operations (C.N.S.: Raw surfaces, open wounds, P.O. drainage tubes).
4. Blood dyscrasia with impaired clotting.
5. Late pregnancy.

Used with caution:

6. Nursing mothers.
7. Severe renal insufficiency.
8. Subacute bacterial endocarditis.
9. Severe hypertension.

be placed in an icebox and tested the next day. If reasonable care is observed in selecting patients for treatment, this procedure is sufficient guarantee for avoiding overdosage in patients whose prothrombin may already be low. Preëxisting hypoprothrombinemia may result in unusual sensitivity of patients to the anticoagulant drugs and thus increased susceptibility to hemorrhagic complications. Again, blood dyscrasias with an impaired clotting mechanism result in a higher incidence of hemorrhage and perhaps a more dangerous type of bleeding. Late pregnancy is a relative contraindication. The anticoagulant drugs may be used with caution in nursing mothers with frequent prothrombin determinations of the infant's blood. Dangerously low prothrombin levels can occur in patients with severe renal insufficiency, as most of the coumarin drugs are excreted via the kidneys. In subacute bacterial endocarditis anticoagulants should be used with caution if other indications for treatment exist. The danger of intracranial hemorrhage is enhanced by use of anticoagulants in severe hypertension.

At the present time the most important single contraindication to the

use of the indandione and coumarin derivatives is lack of satisfactory laboratory control upon which to gauge dosage. Daily individualized charting of the effect of the drug as related to dosage and to the clotting mechanism is recommended. To use these potent drugs otherwise is an invitation to disaster. In table 7 are listed other measures (modified after Bresnick et al.[30]) which may well be considered to insure that these drugs are used efficiently and safely. One consideration which may merit careful thought is the suggestion, if circumstances permit, of delegating the responsibility for anticoagulant administration to one or more specific individuals. In the University of Michigan Hospital this responsibility has been delegated to an "anticoagulant team" composed of a permanent staff member, with associates from the residency training program of the Departments of Medi-

TABLE 7

Commonly Encountered Difficulties of Anticoagulant Therapy in Hospital Practice

In prothrombin testing
Unreliable methods of assay
Inaccuracies (heavy work load; technician rotations)
Test not available on weekends
Confusion of "prothrombin concentration" and "index"
Inconsistent regulation of prothrombin activity
Divided responsibility in house staff
Inexperience:
Failure to individualize therapy
Failure to adjust dosage to prothrombin "trends"
Inadequate treatment period
Failure to obtain blood for testing
Omission of drug
Variation in drug absorption
Differences in drug action and metabolism
Suggestion for solution
Delegate responsibility for anticoagulant therapy to one or two well trained persons. Consistent, careful supervision of dosage and prothrombin levels is the key to safe and effective treatment

cine and Surgery. Daily "rounds" are made by this group who, armed with the information from the laboratory, visit each patient receiving anticoagulants. In this manner individualization of dosage is assured. As a teaching exercise in the field of thrombo-embolic disease, and treatment with anticoagulant therapy, this has proved to be a valuable experience over the course of years. It has also proved to be a satisfactory method, in a large teaching hospital, of obtaining consistent, careful supervision of dosage and prothrombin levels, the key to safe and effective treatment.

USE OF VITAMIN K TO CONTROL EXCESSIVE EFFECT BY COUMARIN AND INDANDIONE DERIVATIVES

The use of coumarin and indandione derivatives has been made considerably safer by the availability of vitamin K. The reliability of the synthetic naphthoquinones, possessing vitamin K-like activity, to reverse the

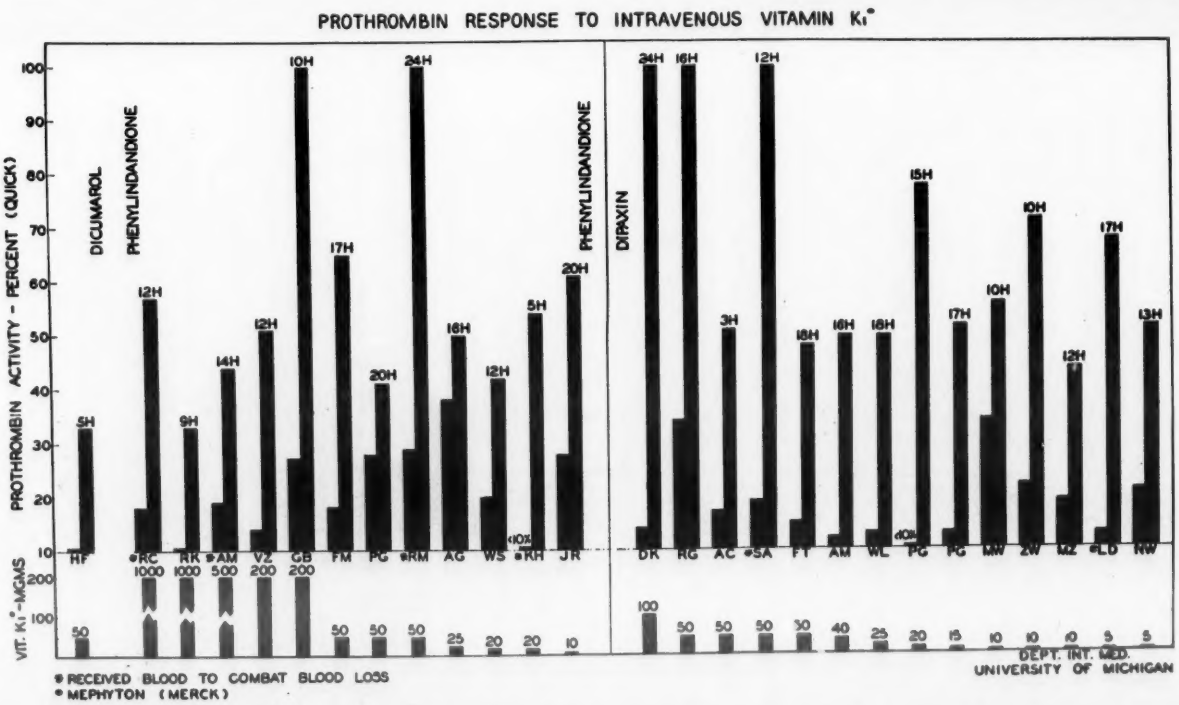


FIG. 4. Prothrombin activity, determined by the Quick method, is expressed in per cent. The first column, in individual cases, shows the initial prothrombin level, while the second shows the response of prothrombin to vitamin K_1, with the time interval at the top of the column. Even with small 5 or 10 mg. doses a safe level of 30 to 40% was reached as rapidly as with massive doses. (Gamble, J. R., Dennis, E. W., Coon, W. W., Hodgson, P., Willis, P. W. III, MaCris, J. A., and Duff, I. F.: Clinical comparison of vitamin K_1 and water-soluble vitamin K, Arch. Int. Med. **95**: 52–58 (Jan.) 1955.)

effect of coumarin derivatives was often disappointing and inconstant. In contrast, there can be little doubt of the effectiveness of oil-soluble vitamin K_1 as an antidote to excessive effect achieved by all known coumarin and indandione derivatives. This vitamin is ineffective against an excessive effect from heparin.

Oil-soluble natural vitamin K_1 is available commercially as an emulsion. It is prepared for intravenous injection. When used intravenously, the emulsion of K_1 must be injected slowly; dilution with strong electrolytic solutions is to be avoided, since they may disturb the emulsion state of the

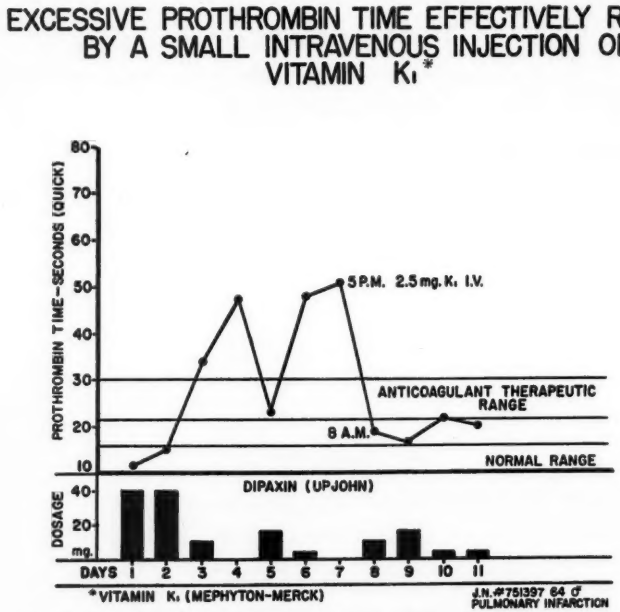


FIG. 5. In this patient prothrombin time was excessively prolonged by the anticoagulant: a satisfactory effect was restored by the intravenous injection of a small dose of vitamin K_1, thus permitting continuation of therapy without the development of resistance to the anticoagulant.

product. Of considerable interest is the fact that this emulsion is effective when administered by mouth. It is hoped that in the near future a tablet preparation of vitamin K_1 will be available for oral use. There is some indication that intramuscular injection of vitamin K_1 may be ineffective.[32] Whether vitamin K_1 may produce a state of hypercoagulability requires further study; there can be no doubt, however, of the potency of the preparation in rapidly reversing the defect in the coagulation mechanism achieved with oral anticoagulants. In view of this, it would appear reasonable to employ minimal yet effective doses of this potent drug.

Figure 4 shows the effect [81] of vitamin K_1 when given intravenously or by mouth to a series of patients who had received oral anticoagulants. Prothrombin activity, determined by the Quick method, is expressed in per cent. In each instance the first column shows the initial prothrombin level and the second column the response to the vitamin K_1, with the time interval indicated at the top of the second column. It is evident that even with small, 5 or 10 mg. doses a safe level (defined as 30% or preferably 40%) is reached as rapidly as with massive doses; this is equally true with regard to response to oral administration. When treatment is to be continued, even smaller doses—1 to 2 mg. given orally—serve to raise the prothrombin concentration to therapeutic levels; this permits continuation of therapy without the resistance to the anticoagulant seen after administration of the larger doses generally recommended (figure 5).

Recommendations as to dosage of vitamin K_1 are indicated in table 8. If there is excessive prothrombin depletion but no bleeding, 1 to 5 mg. orally

TABLE 8

Anticoagulant Therapy Use of Vitamin K_1*

Excessive prothrombin depletion but no bleeding
Vitamin K_1: 1 to 5 mg. oral

Minor hemorrhage (treatment to be continued)
Vitamin K_1: 10 mg. oral

Major hemorrhage
Vitamin K_1: 50 mg. I.V.
Single injection usually produces satisfactory prothrombin effect in 4 hours
Whole blood or plasma as required

* Mephyton—Merck.

may be given. If there is minor hemorrhage and treatment is to be continued, 10 mg. of vitamin K_1 may be given orally. With major hemorrhage, 50 mg. of K_1 intravenously in a single injection will produce a safe level, usually in four hours; this dose may be repeated if necessary. Whole blood or plasma should be used as required. Essentially similar recommendations with regard to vitamin K_1 dosage have been made by others.[83]

PREVENTION OF EXCESSIVE EFFECT BY HEPARIN

With the exception of preparations of coumarins for intravenous injection (Coumadin and Marcumar), heparin is the only available parenteral anticoagulant. Heparin, for practical purposes, is ineffective when given by mouth. This sulfurated polysaccharide, derived from animal sources, is still expensive; search thus continues for a synthetic polysaccharide with heparin-like effect. Dextran sulfate, a synthetic polysaccharide with heparin-like qualities, currently being investigated,[84] appears to offer promise.

Heparin produces a marked and immediate effect on the clotting mecha-

nism in a manner entirely different from that of the coumarin drugs.[28] Its effect, which is directly correlated with its concentration in the blood, is measured by the Lee and White method [35] of blood clotting time determination. This procedure is performed at the bedside. In normal subjects the Lee and White clotting time may vary from five to 15 minutes. Although the test is very gross, it may be depended upon to reflect the anticoagulant effect of heparin. Olwin [17] employs the Quick one-stage prothrombin test as a measure of the effect of heparin.

The experimental evidence that heparin favorably retards intravascular clotting is confusing and sometimes conflicting.[36, 43] The minimal degree of prolongation of the coagulation time by the drug which indicates an anticoagulant effect sufficient to prevent thrombosis has not been established.[37] For clinical use, upon the basis of investigative work in animals,[38] it is generally conceded that prolongation of the clotting time to a value twice the normal (that is, into the range of 14 to 20 minutes) is evidence of a definite and satisfactory effect of heparin on the clotting mechanism.

Alternative methods of administering heparin are available.[39, 46] It may be injected directly into a vein, and thereby produce an immediate and striking effect upon the clotting time (table 3). The extent and duration of clotting time prolongation achieved are related to dosage; generally, however, this has vanished four to six hours later. If the injection is repeated at appropriate intervals a picket-fence effect is achieved on the clotting time. A more moderate and sustained effect may be obtained by continuous infusion of heparin, the control of which depends upon clotting time determinations. Subcutaneous and intramuscular injection of heparin may produce a measurable effect upon the clotting time for upwards of 12 to 18 hours. As far as is known, there is no proof that the therapeutic effect of heparin, insofar as it applies to the prevention or treatment of thrombo-embolic disease, is correlated with the constant or inconstant effect it produces on the clotting mechanism. It is probably true that in most cases, regardless of the method of administration, an erratic effect on the clotting time is produced by heparin. Clotting time determinations, however, are advisable when this anticoagulant is administered to patients about whom there may be doubt concerning the integrity of the hemostatic mechanism, in which case too marked prolongation of the clotting time is to be avoided. Clotting time determinations are also advisable when the drug is administered by subcutaneous or intramuscular injection since, in some instances, local inactivation may occur and explain lack of measurable effect upon blood coagulation.

The indications for the use of heparin may be simply defined; it is the drug of choice: (1) in those instances where an anticoagulant effect is desired but where circumstances make the use of coumarin or indandione derivatives unwise or impractical; (2) where an immediate effect upon the clotting mechanism is desired. Heparin is frequently administered in conjunction with oral anticoagulants, being discontinued when these prepara-

tions have achieved a satisfactory effect upon the clotting mechanism. In respect to the combined use of these anticoagulants, it is well to keep in mind that if blood is drawn for prothrombin testing at a time when appreciable amounts of heparin are present, the latter drug may produce prolongation of the Quick prothrombin time (table 3). To avoid this, blood for prothrombin estimation, upon which coumarin dosage is to be estimated, should be obtained not sooner than four hours after intravenous heparin and about 12 to 16 hours after intramuscular or subcutaneous administration. Needless to say, in initiating combined therapy the needle used to draw heparin into a syringe should not then be employed to obtain blood for a baseline

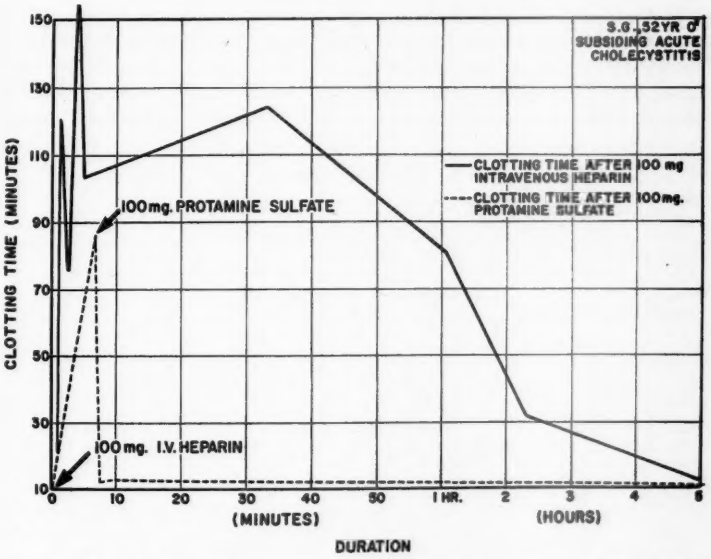


FIG. 6. The effect on the clotting time after 100 mg. intravenous heparin by 100 mg. of intravenous protamine sulfate.

prothrombin prior to injecting the heparin. Sufficient heparin may cling to the needle to produce erroneous prolongation of the prothrombin time and hence to make the baseline value worthless. The effect of heparin on the Quick prothrombin time is illustrated in table 3; this is contrasted with the absence of effect on the prothrombin activity as determined by the modified Owren method. This suggests an advantage in the latter method for following patients when the coumarin derivatives and heparin are being administered simultaneously.

Untoward immediate allergic reactions have followed intravenous injections of heparin.[41] These are fortunately very rare; to avoid them, how-

ever, the drug should be injected slowly into a vein over the course of one or two minutes. In the event the patient is suspected of being or known to be sensitive to heparin, the drug should be employed with great caution, if at all.

Heparin may produce variable types of bleeding, of which local ecchymoses and wound bleeding are probably the most common examples. Bleeding attributed to heparin may be promptly and dramatically checked by the intravenous injection of protamine sulfate (figure 6). In the event heparin has been given by vein, slow intravenous injection of 50 mg. protamine sulfate will usually suffice for this purpose. This dosage may require repetition after intramuscular injection because of further release of the anticoagulant from the local deposit. In practice, the incidence of bleeding associated with the use of heparin is very low. Unless the hemorrhage is of major proportion protamine sulfate is usually not required, since the effects of heparin, if it has been given by vein in the usual dose, will have disappeared within a matter of six hours and the bleeding will have ceased.

Discussion

Although anticoagulant therapy has been available to clinicians for a number of years, important problems are still associated with this method of treating or preventing thrombo-embolic disease. The primary problem appears to be control of excessive effect by these potent agents.

With the continuing search for the ideal anticoagulant, the clinician is confronted by an ever increasing number of potent drugs, none of which is entirely satisfactory but from which selection of the drug of choice must be made. Regardless of which anticoagulant is selected, careful attention should be given to its pharmacologic properties and the respects in which it differs from other anticoagulants, especially Dicumarol. It is highly desirable, particularly for those unfamiliar with this field, to become thoroughly familiar and experienced with one drug. If, in the past, Dicumarol has adequately served the clinician, the newer coumarin or indandione derivatives do not appear to possess sufficient virtue to displace the use of the older anticoagulant. If one has become dissatisfied with Dicumarol or wishes to try out the newer preparations, phenylindandione has proved a satisfactory drug for use in hospitalized patients.

Dosage of the coumarin and indandione derivatives is based upon daily and careful determination of plasma prothrombin activity. In our opinion, the Quick one-stage procedure remains a suitable laboratory procedure for this purpose. Three satisfactory, but different, expressions of prothrombin activity, based upon the Quick procedure, are available for estimation of dosage to achieve the therapeutic goal with the coumarin and indandione derivatives.

There is lack of agreement with respect to what constitutes an "adequate effect" with anticoagulant drugs. For the present the clinician, after delib-

eration, must decide the degree of alteration of the clotting mechanism which he wishes to achieve, and perhaps the method of prothrombin determination upon which this is to be based. For the treatment of active intravascular clotting the alterations of prothrombin advocated by Allen and Wright, based on the Quick procedure, are comparable. There appears to be fairly satisfactory correlation between prothrombin determinations as obtained by the two-stage and by the Quick methods. Hence, the therapeutic goal advocated by Olwin, based on the two-stage procedures, is also similar to that of Allen and Wright. The goal advised and achieved by Owren and by Ware and Griffith is not, however, comparable to that advocated by Allen, Wright and Olwin. Characteristics of the Owren P and P method and of the Ware modification of the Owren method are responsible for the fact that the therapeutic range or degree of alteration induced in the clotting mechanism by anticoagulants by these procedures is considerably less drastic than that achieved after the method of Allen and Wright and Olwin. In spite of this, it becomes significant that Owren and Ware and Griffith achieve a satisfactory therapeutic effect; moreover, the danger of hemorrhage is also apparently less when the clotting mechanism is more moderately altered. Need exists for detailed study of this problem and apparent conflict. Smith [29] and associates have emphasized the underlying problem; such investigations may well bring about revision in the accepted goal commonly sought with anticoagulants. The fact, too, that the coumarin and indandione derivatives alter other factors in the clotting mechanism, perhaps before prothrombin is significantly reduced, requires exploration.

Careful attention must be paid to the selection of suitable candidates for anticoagulant therapy. The hazard of bleeding, in certain circumstances, is considerably increased by unwise administration of anticoagulants. In those patients selected for treatment, careful and individualized supervision of dosage and prothrombin levels, based upon carefully performed laboratory procedures, is the crux to safe and effective administration of these potent agents. If circumstances permit, this goal may perhaps be achieved by delegating the specific responsibility for anticoagulant administration to one or more individuals or an "anticoagulant team."

Excessive effect upon prothrombin activity, with or without bleeding, may complicate the administration of the coumarin and indandione derivatives by even the most experienced and conscientious clinician. Watchful expectation and judicious use of the antidote, vitamin K_1, have considerably lessened this hazard. A potent antidote, protamine sulfate, is available to combat the excessive effect of heparin.

Summary

Anticoagulant therapy has not yet reached the ideal state in which complications are unknown. Hemorrhage is an ever present danger. Its incidence can be minimized by knowledge of the tests employed to control ad-

ministration of these drugs. Therapeutic levels should be determined which prevent intravascular thrombosis and are associated with a minimal incidence of hemorrhage. When hemorrhage or the possibility of hemorrhage occurs due to coumarin and indandione derivatives, vitamin K_1 is a most effective antidote. Protamine sulfate is immediately effective in reversing the prolonged clotting time due to excessive administration of heparin. Upon the basis of experience and careful clinical judgment in selection of patients, effective anticoagulant therapy can be achieved and its excessive effects can be largely avoided.

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SUMMARIO IN INTERLINGUA

Le subjugation de effectos excessive—e assi de hemorrhagias—es un importante problema associate con le therapia a anticoagulantes. In su continue cerca del agente ideal, le clinico se trova confrontate con le problema de seliger le plus promittente anticoagulante ex un plethora de potente drogas. In general, le plus recente derivatos de coumarina e indandiona non pare posseder virtutes sufficiente pro justificar le rejection del derivatos plus ancian, como per exemplo Dicumarol, con que le clinico ha possibilemente jam un prolongate experientia.

Le dosage del derivatos de coumarina e indandiona es basate super caute e repetite determinationes del activitate "prothrombinic" del plasma. Le ben executate technica uniphasic de Quick es generalmente considerate como convenibile pro iste objectivo. Es derivate ab iste test tres satisfacente sed differente expressiones del activitate prothrombinic le quales pote servir como base del estimation del dosage del droga a usar. Le activitate prothrombinic es etiam mesurabile per le methodo uniphasic de Owren (le methodo P e P [prothrombina e proconvertina]) o de Ware (un modification del methodo de Owren). Illo pote etiam esser mesurate per le methodo biphasic (le modification del test de Warner, Brinkhouse, e Smith, elaborate per Seeger). Le grado del effecto anticoagulante que debe esser designate como un "effecto adequate" non es le mesme secundo mesurationes executate per le mentionate quatro methodos. In le administration oral de anticoagulantes il pare haber un satisfacente correlation quando le activitate prothrombinic es mesurate per o le methodo biphasic o le methodo de Quick. Un alteration considerabilemente minus drastic es inducite in le mechanismo coagulative si le mesurationes es effectuate secundo le methodos de Owren e de Ware, sed il pare nonobstante que le resultante effecto therapeutic es equalmente satisfactori, e le risco de hemorrhagias es considerabilemente reducite. Le clinico debe decider se qual grado de alteration del mechanismo coagulative ille vole producer per medio de anticoagulantes, e in certe casos ille debe seliger le methodo del determination del activitate prothrombinic super le qual su procedimento va esser basate.

Grande attention debe esser prestate al selection del patientes pro qui le therapia a anticoagulantes es recommendabile. Sub certe conditiones le incaute administration de iste drogas augmenta grandemente le risco de hemorrhagias. Le caute e individualisate surveliantia del dosage e del effecto de iste dosage super le mechanismo coagulative es le clave al efficace e non-riscose administration del derivatos de coumarina e indandiona. Vitamina K_1 es un efficacissime antidoto de lor effectos excessive. Le

associate risco de hemorrhagias es grandemente reducite per le judiciose administration de vitamina K_1 per via oral o per via intravenose.

Ab le puncto de vista del predicibilitate del effecto exercite super le mechanismo coagulative, heparina es un droga de administration difficile. Il es probabile que sin reguardo al modo de su administration, le effecto de heparina super le tempore de coagulation es erratic in le majoritate del casos. Nonobstante, determinationes del tempore coagulative (Lee-White) es recommendabile quando heparina es administrate a patientes in qui le integritate del mechanismo hemostatic non es libere de suspicion. Un potente antidoto pro subjugar le effecto excessive de heparina es disponibile in le forma de sulfato de protamina.

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HIGHLY POTENT ADRENAL CORTICAL STEROIDS: STRUCTURE AND BIOLOGIC ACTIVITY *

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SYNTHETIC adrenal steroids possessing biologic activity greater than that of the naturally occurring secretory products of the adrenal cortex are of considerable theoretic importance and, in certain instances, may offer unusual opportunities for hormone therapy. Furthermore, it is of particular interest that the isolation and identification of a very active, naturally occurring sodium-retaining adrenal steroid (aldosterone) should have coincided with the synthesis of derivatives of hydrocortisone possessing physiologic activities manyfold greater than those of any previously known naturally occurring steroid. In 1954 Reichstein announced the identification and crystallization of "aldosterone," a naturally occurring adrenal steroid first described by Simpson and Tait as "electrocortin." [1, 2] Clinical studies with this substance have necessarily been limited by the very small quantity of material thus far available for clinical use. There is no doubt, however, concerning the high degree of electrolyte-regulating potency which it possesses.[3, 4] In 1953 and 1954 Fried and Sabo, while attempting to synthesize hydrocortisone from 11-epi-17-alpha-hydrocortisone by way of a halogenated intermediate, found that the 9-alpha-chloro- and fluoro-derivatives of hydrocortisone were highly active in the rat liver glycogen assay for 11-oxygenated corticoids.[5] Further studies by Borman, Singer and Numerof [6] indicated that these compounds possessed, in addition, marked sodium-retaining activity. More recently, Herzog et al.[7] have described the preparation of Δ1-derivatives of cortisone and hydrocortisone (metacortandracin † and metacortandralone †); preliminary clinical evaluation indicated that these compounds exhibited enhanced anti-inflammatory potency with little or no salt-retaining activity.[8]

In this investigation an attempt has been made to compare the physiologic activity of these groups of steroid derivatives with the well established therapeutic agent, hydrocortisone. *"Sodium-retaining"* or *"inorganic metabolic-regulating"* activity in this study refers to the capacity of a compound to reduce renal excretion of sodium in adrenalectomized animals or in pa-

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† Also designated as prednisolone (Δ1-hydrocortisone) and prednisone (Δ1-cortisone).

tients with Addison's disease, with consequent clinical improvement. Obviously the administration of toxic substances may result in decreased renal excretion of sodium; however, in this instance one observes a marked shortening of the survival period of adrenalectomized animals. *"Carbohydrate-regulating"* or *"organic metabolic-regulating"* potency refers to the principal, and apparently interdependent, actions exhibited by hydrocortisone and cortisone, i.e., the capacity to maintain a normal blood sugar level with increased gluconeogenesis, to induce eosinopenia, lympholysis, leukocytosis, and an increase in hemoglobin and red blood cell levels, to establish a normal electroencephalogram and myogram, to increase gastric secretions, and to restore the capacity of the organism to respond to a water load with a prompt diuresis. It is entirely possible that, in the future, compounds may be prepared in which a high degree of specific enhancement of one or more of these physiologic effects is achieved. To date the "anti-inflammatory" activity of adrenal steroids parallels in general their "carbohydrate-regulating" and "pituitary-inhibiting" activity.

Whereas the modification of a steroid molecule leading to marked enhancement of any physiologic activity is of great theoretic interest, a broader spectrum of therapeutic usefulness is more likely to be associated with the enhancement of the ratio of organic metabolic-regulating activity to inorganic or salt-retaining potency. Because of these important therapeutic implications, an attempt has been made to estimate the *relative potentiation* of organic versus inorganic metabolic-regulating potency of 9α-fluorohydrocortisone, delta-1-hydrocortisone and aldosterone, using hydrocortisone as a point of reference.

Methods

The studies were carried out on the metabolic ward of the Peter Bent Brigham Hospital, with the assistance of Miss Frances W. Bowen and Miss M. Constance McCarthy. The 17-hydroxycorticoids were determined by the method of Reddy, Jenkins and Thorn.[9] The 17-ketosteroids were determined by a modification of the method of Drekter et al.,[10] whereby the colorimetry was performed as in the procedure of Holtorff and Koch.[11] Chemical determinations on blood and urine and eosinophil counts were carried out by methods previously described.[12] Changes in the urinary excretion of sodium and potassium have been used as a basis for the comparison of mineralocorticoid activity of these compounds. The urinary excretion of true glucose,[13] nitrogen and uric acid, the change in circulating eosinophils and the inhibition of endogenous adrenal secretion have been employed as the indices of organic metabolic potency.

Observations

9α-Fluorohydrocortisone: The structural formula of this compound is given in figure 1. Studies in rats [6] had indicated that 9α-fluorohydrocorti-

sone was twice as active as desoxycorticosterone acetate with regard to its sodium-retaining activity, while its carbohydrate activity was eight times that of cortisone acetate. Preliminary studies suggest a further enhancement of the sodium-retaining activity in man.[14, 15] The marked inorganic-metabolic effects of 9α-fluorohydrocortisone are shown in figure 2. It is apparent that in this instance 5 mg. of 9α-fluorohydrocortisone given as a single dose by mouth were considerably more effective than 100 mg. of hydrocortisone similarly administered to a patient with Addison's disease. It is of particular interest that sodium retention, potassium diuresis and the

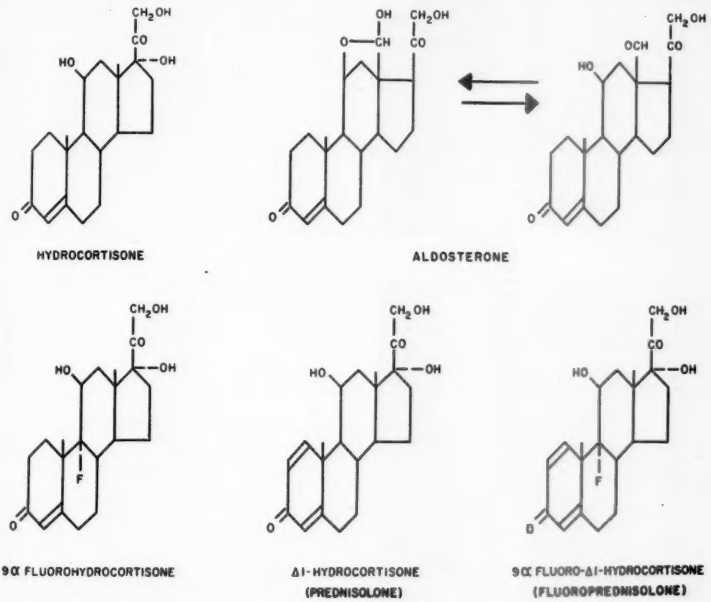

FIG. 1.

profound decrease of urinary sodium: potassium ratio were more prolonged in the case of the fluorinated compound.

A 25 year old male subject on a constant diet was given an intravenous infusion of 100 mg. of hydrocortisone in 500 ml. of physiologic salt solution over an eight hour period and under fasting conditions. Blood was taken at two hour intervals for the determination of eosinophils and glucose. Sodium, potassium and uric acid were measured on urine specimens collected every two hours during the period of infusion. Forty-eight hours later the experiment was repeated, employing 2 mg. of 9α-fluorohydrocortisone. The observations are summarized in figure 3. It is apparent that 2 mg. of

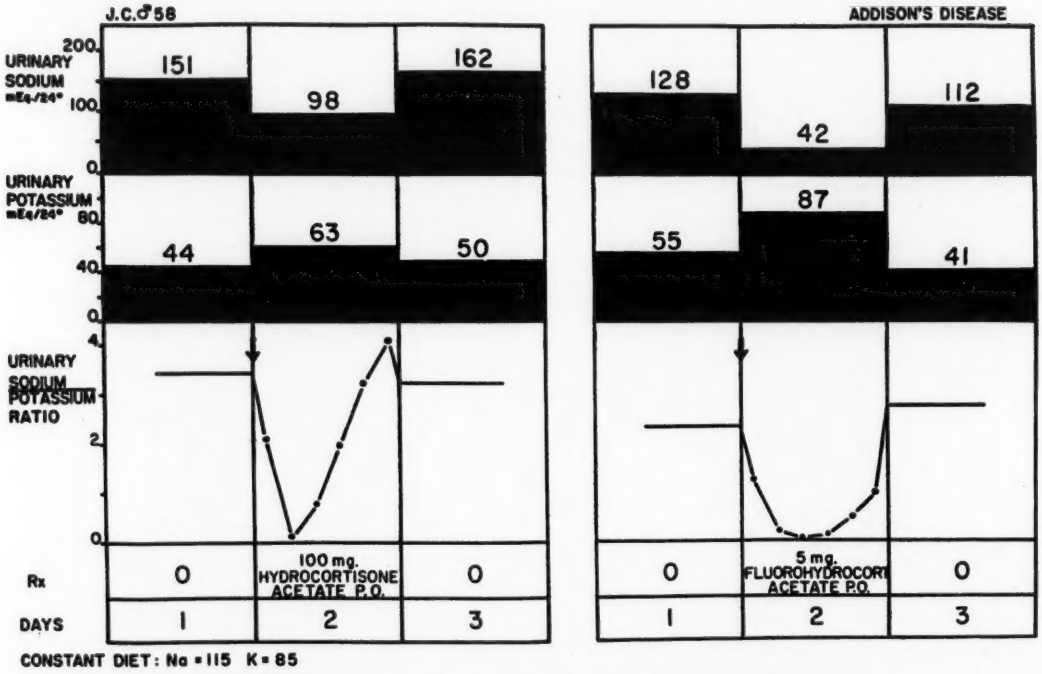

FIG. 2. Comparative effects of hydrocortisone and 9-alpha fluorohydrocortisone.

HYDROCORTISONE			FLUOROHYDROCORTISONE		

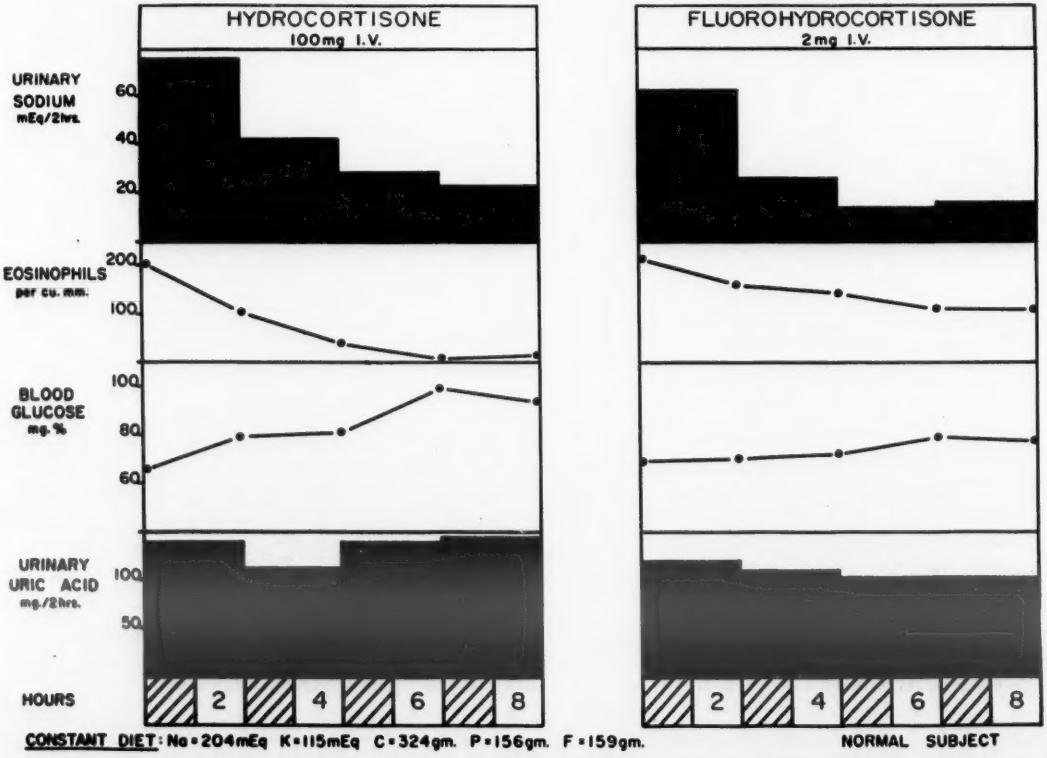

FIG. 3. Comparative effects of hydrocortisone and 9-alpha fluorohydrocortisone.

9α-fluorohydrocortisone exerted a sodium-retaining effect greater than that obtained with 100 mg. of hydrocortisone. Further studies indicated that fluorohydrocortisone is at least 50 times as active as hydrocortisone in its electrolyte-regulating capacity. With regard to the organic metabolic-regulating activity of fluorohydrocortisone, it is to be noted that in the same experiment 2 mg. of 9α-fluorohydrocortisone were not equal in potency to 100 mg. of hydrocortisone, as indicated by the change in circulating eosinophils, the rise in fasting blood glucose level and the excretion of urinary uric acid. Subsequent studies carried out in normal subjects and in patients with Addison's disease suggest that the organic-regulating potency of 9α-fluorohydrocortisone is approximately 20 times as great as that of hydrocortisone. Thus, in this instance the insertion of a fluorine atom in the 9α position has resulted in a marked potentiation of activity of the parent compound. However, the overall changes indicate a decrease in the ratio of organic to inorganic metabolic-regulating potency, as illustrated in figure 4. In general, an alteration of ratio of activity in this

	"SUGAR" ACTIVITY	"SALT" ACTIVITY	"SUGAR/SALT" RATIO
HYDROCORTISONE	1	1	1
9α FLUOROHYDROCORTISONE	20	50+	0.4
Δ1-HYDROCORTISONE	4	1	4.0
Δ1-9α FLUOROHYDROCORTISONE	20	50+	0.4
ALDOSTERONE	21	50+	0.02

FIG. 4. Relative potency of some adrenal cortical steroids in man (estimated).

direction limits the widespread use of a compound as an effective anti-inflammatory agent. On the other hand, the synthesis of a compound exhibiting 20 times the activity of the parent compound in organic metabolic-regulating potency and in pituitary-inhibiting capacity (vide infra and figure 12) provides an extremely interesting tool in the evaluation of endogenous ACTH and adrenal cortical secretory activity. Further observations on this aspect of fluorohydrocortisone will be presented.

Δ1-Hydrocortisone (Metacortandralone) and Δ1-Cortisone (Meticorten): Earlier reports by Bunim et al.[8] indicated that the introduction of a double bond between carbon 1 and 2 of hydrocortisone or cortisone (figure 1) enhanced the anti-inflammatory potency of these substances. These authors reported the remarkable observation that Δ1-hydrocortisone and Δ1-cortisone appeared to have little or no sodium-retaining activity. For this reason it appeared of interest to compare Δ1-hydrocortisone and Δ1-cortisone with hydrocortisone, cortisone, 9α-fluorohydrocortisone and aldosterone.

FIG. 5. Comparative effects of hydrocortisone and Δ1-hydrocortisone (metacortandralone).

A 40 year old male subject with normal adrenal function, maintained on a constant diet, was given an eight hour intravenous infusion of 50 mg. of Δ1-hydrocortisone (figure 5). During the initial 24 hour period sodium excretion was reduced appreciably, i.e., from a level of 102 mEq. per 24 hours to a level of 72 mEq. per 24 hours. Continued and enhanced sodium retention occurred in the second 24 hour period following the single initial eight hour infusion of 50 mg. of the Δ1-compound, sodium excretion falling

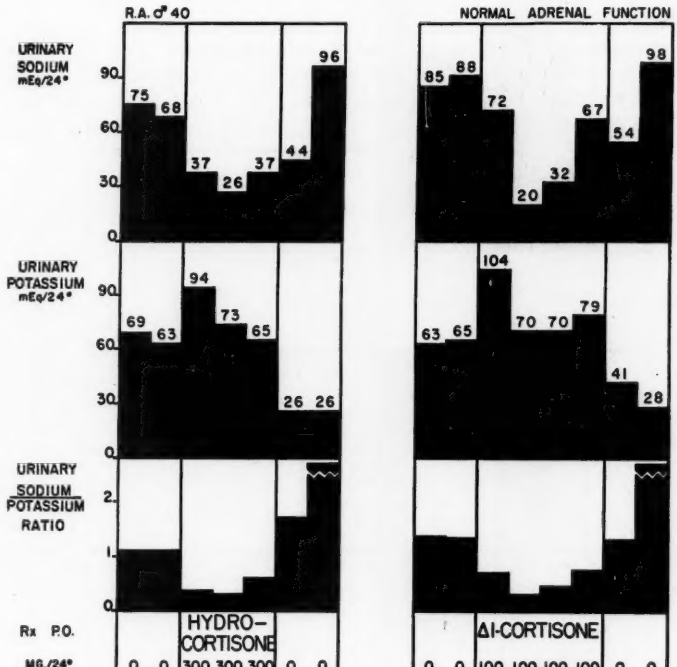

FIG. 6. Comparative effects of hydrocortisone and Δ1-cortisone (metacortandracin).

to a level of 53 mEq. per 24 hours. During the third 24 hour period an escape in sodium excretion was observed. Increased potassium excretion was noted during the first 24 hour period, with a definite rebound in the second 24 hour period. In summary, a single eight hour infusion of 50 mg. of Δ1-hydrocortisone resulted in definite and prolonged sodium retention, with an appreciable but transient increase in potassium excretion and with the anticipated fall in urinary Na/K ratio. In the same subject a single

eight hour infusion of 200 mg. of hydrocortisone resulted in marked sodium retention during the first 24 hour period. Maximal changes in the urinary Na/K ratio were attained somewhat more rapidly (figure 5) than with the Δ1 compound. The magnitude of the sodium retention with hydrocortisone (200 mg.) was similar to that observed with 50 mg. of Δ1-hydrocortisone.

Subsequently subject R. A. was given Δ1-cortisone in a dose of 25 mg. by mouth every six hours for a total period of four days. At this relatively high dose level, sodium retention was again noted (figure 6). Maximal sodium retention was not attained until the second day, and persisted for 24 hours following the discontinuance of the hormone. With orally administered Δ1-cortisone a transient but definite increase in urinary potassium excretion occurred.

Further studies of the sodium-retaining effect of Δ1-hydrocortisone and Δ1-cortisone were carried out on six patients with Addison's disease and on one normal subject. Although well marked sodium retention had been obtained in the studies just described, this was not a consistent finding, and an adequate estimate of the salt-retaining potency of Δ1-hydrocortisone as compared with the parent compound could not be made. This is not surprising when one considers that whenever this highly potent carbohydrate-active corticoid is administered, urinary sodium excretion reflects the balance between two separate effects of the hormone.[16] First, the marked carbohydrate activity results in an increased glomerular filtration rate, with a resulting increase in the sodium load presented to the tubule for reabsorption. Second, the salt-retaining activity of the compound leads to increased tubular reabsorption of sodium. Whereas the latter effect may be expected to be rather constant from individual to individual, and to depend mainly on the salt-retaining potency of the administered steroid, the increase in glomerular filtration rate varies greatly from individual to individual, both as to magnitude and as to appearance in time. It is therefore to be expected that for compounds with a shift of the ratio of carbohydrate activity to salt-retaining activity towards the former, a wide scatter of estimates of salt-retaining activity will be observed. The only conclusion which appears to be warranted at the present time is that Δ1-hydrocortisone and Δ1-cortisone do indeed have definite sodium-retaining activity and that it is of approximately the same order of magnitude as that of hydrocortisone.

In these same experiments quantitation of the organic metabolic-regulating activity of Δ1-hydrocortisone and Δ1-cortisone was attempted. The eosinophil response and the changes in urinary glucose and uric acid excretion which in subject R. A. followed the intravenous administration of 50 mg. of Δ1-hydrocortisone are shown in figure 7 and are compared with the effect of 200 mg. of hydrocortisone similarly administered. The overall changes produced by the two substances were almost identical, and it would appear that the organic metabolic-regulating activity of the Δ1-com-

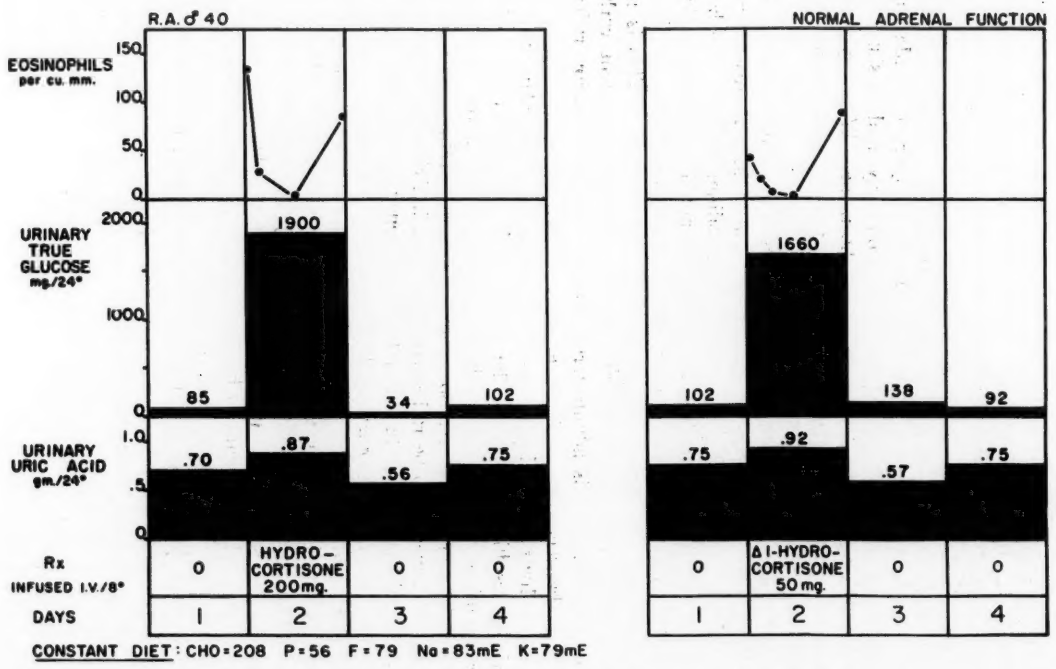

FIG. 7. Comparative effects of hydrocortisone and Δ1-hydrocortisone (metacortandralone).

pound was in this instance increased by a factor of 4 as compared with hydrocortisone. During the period in which subject R. A. received 25 mg. of Δ1-cortisone by mouth every six hours for four days, an immediate reduction in circulating eosinophils, with virtual absence during the four day period of therapy, was noted (figure 8), a change which paralleled the findings in this same subject given 300 mg. of hydrocortisone daily for

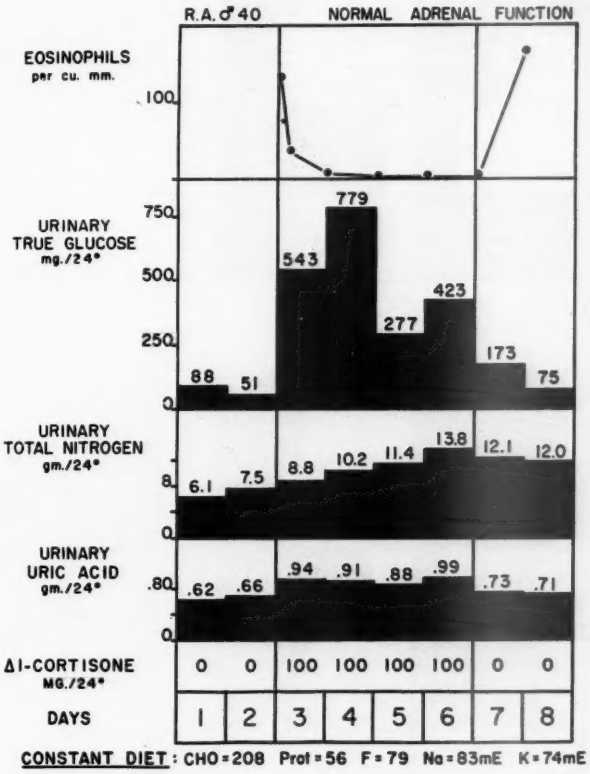

FIG. 8. Effect of Δ1-cortisone (metacortandracin) on organic metabolism.

three days. Of great interest during the period of Δ1-cortisone administration was the markedly and persistently enhanced total nitrogen excretion. Similarly, an increase in uric acid excretion and in true urinary glucose excretion occurred. The magnitude of the increased nitrogen excretion observed in this study with 100 mg. of Δ1-cortisone daily definitely exceeded that occurring in this same subject when given 300 mg. of hydrocortisone by mouth on three successive days. Again it would seem warranted to

FIG. 7. Comparative effects of hydrocortisone and Δ1-hydrocortisone (metacortandralone).

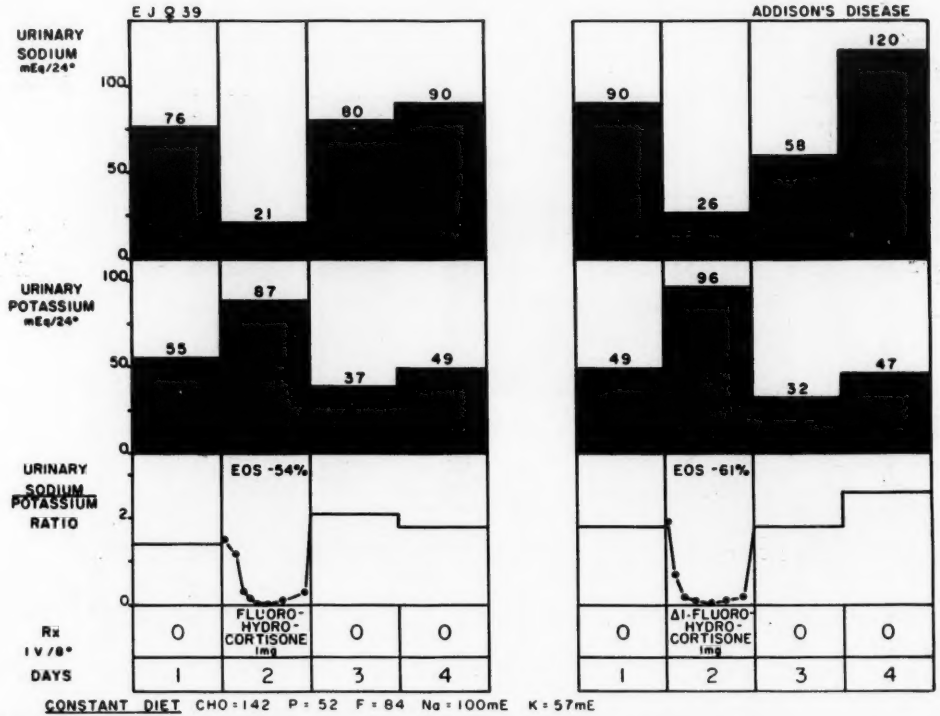

FIG. 9. Effects of fluorohydrocortisone and Δ1-fluorohydrocortisone.

conclude that the organic metabolic-regulating activity of Δ1-cortisone is approximately four times that of hydrocortisone.

It can be readily seen that, in comparison to fluorohydrocortisone, in which the electrolyte-regulating activity of hydrocortisone has been increased by a factor of 50 or more and the carbohydrate-regulating activity by a factor of 20, the Δ1-hydrocortisone is considerably less active physiologically. However, in the case of the latter compound the relative increase in organic metabolic-regulating activity over and above that of the sodium-retaining factor is a distinctive feature which improves the therapeutic index for those generalized diseases in which an anti-inflammatory response is desired and in which excessive sodium retention constitutes a limiting factor (figure 4).

Δ1-Fluorohydrocortisone: Very recently Fried and his collaborators were able to prepare a small quantity of the 9α-fluorinated derivative of Δ1-hydrocortisone (figure 1). The activity of this compound has been studied in one patient with normal adrenal function and in three patients with Addison's disease. An estimate of the sodium-retaining activity of Δ1-fluorohydrocortisone was obtained by comparing the effect of 1 mg. administered intravenously over eight hours with that of 1 mg. of fluorohydrocortisone, of 50 mg. of hydrocortisone, and of 12.5 mg. of Δ1-hydrocortisone, all similarly administered. This comparative study was carried out in two of the patients with Addison's disease, and the effects of Δ1-fluorohydrocortisone and fluorohydrocortisone in one of them are illustrated in figure 9. It is apparent that the effect of either compound on sodium and potassium excretion and on the urinary sodium-to-potassium ratio was almost identical. At this dose level, the organic metabolic-regulating effects of the two compounds were small, and were mainly evidenced by a depression of the circulating eosinophil level at the end of the infusions. The magnitude of this depression was the same for both compounds.

The effectiveness of Δ1-fluorohydrocortisone on carbohydrate metabolism was best measured by comparing the effects of a larger dose (10 mg.) with that of 200 mg. of hydrocortisone in subject R. A. The changes in circulating eosinophils and in the urinary excretion of true glucose and of uric acid are shown in figure 10. It can be seen that the overall effects of 10 mg. of Δ1-fluorohydrocortisone were quite similar to those of 200 mg. of hydrocortisone. The activity of Δ1-fluorohydrocortisone as measured by the inhibition of spontaneous adrenal activity was also compared with that of fluorohydrocortisone and will be reported further on (figure 12).

It would therefore appear that, as compared with hydrocortisone, Δ1-fluorohydrocortisone exhibits an increase in inorganic metabolic-regulating activity by a factor of 50 or more, and of organic metabolic-regulating activity by a factor of approximately 20. The compound would therefore appear to be very similar in its biologic activity to fluorohydrocortisone. These preliminary studies suggest that a marked increase in both inorganic- and organic-regulating activity has been attained at the expense of a decrease

FIG. 9. Effects of fluorohydrocortisone and Δ1-fluorohydrocortisone.

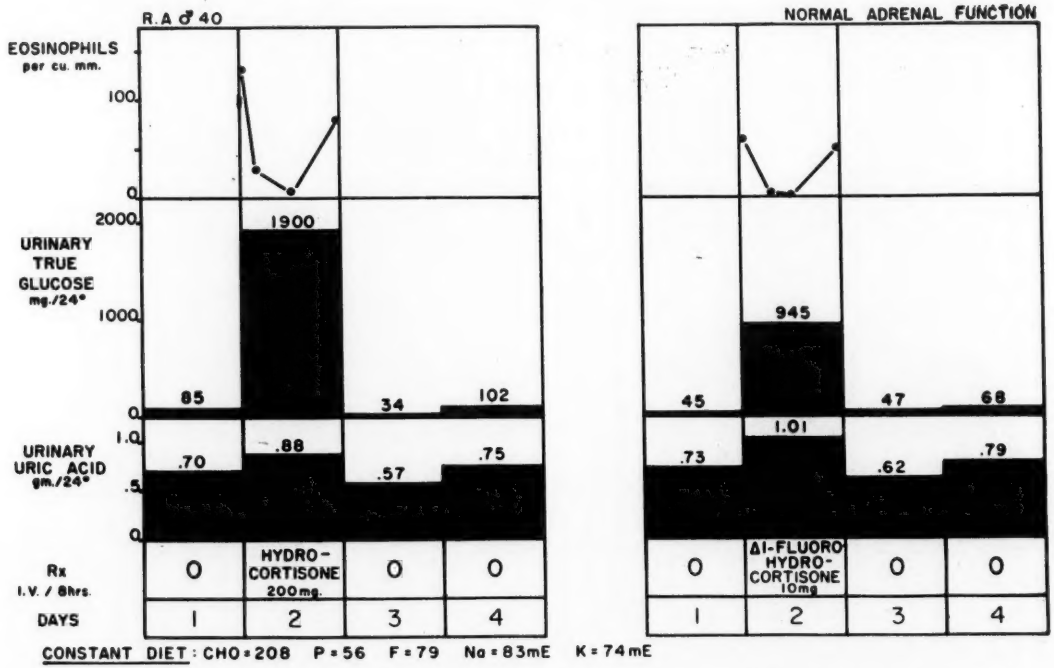

FIG. 10. Effects of hydrocortisone and Δ1-fluorohydrocortisone.

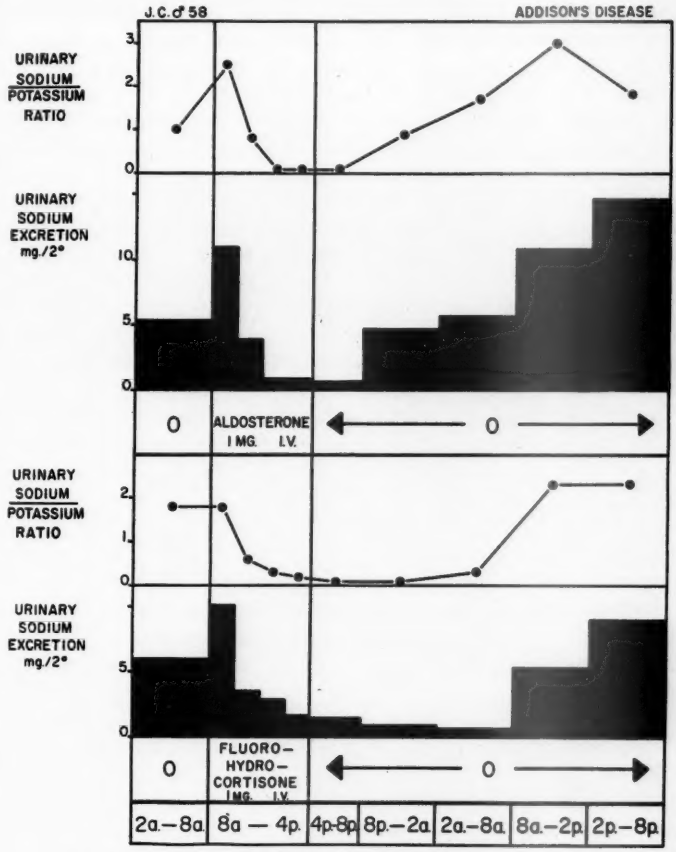

FIG. 11. Comparative effectiveness of intravenous aldosterone and 9 alpha-fluorohydrocortisone.

in therapeutic index due, in this instance, to the relatively greater potentiation of salt-retaining activity which accompanies the insertion of a 9α-fluoro grouping (figure 4).

Aldosterone: Having had the opportunity to study the physiologic action of highly potent synthetic adrenal steroids, the authors were fortunate to have available a small quantity of naturally occurring crystalline aldosterone (figure 1). The earlier studies of Mach [8] had confirmed in man the high degree of electrolyte-regulating potency which this compound had been shown to exhibit in animal studies. The present study was carried out

to clarify the quantitative relationship of the sodium-retaining effect of aldosterone as compared to that of fluorohydrocortisone and Δ1-fluorohydrocortisone and, in addition, to ascertain whether aldosterone possessed any appreciable organic-regulating potency in physiologic or near-physiologic doses in man. Animal studies had indicated that aldosterone possesses approximately one third the carbohydrate metabolic-regulating activity of cortisone, milligram for milligram.[4]

Earlier studies [17] indicated that in a patient with Addison's disease 200 micrograms of aldosterone administered intravenously over a four hour period resulted in a rapid and profound decrease in sodium excretion and an increase in potassium excretion. The intensity of this effect was equal to that observed with a similar quantity of 9α-fluorohydrocortisone. However, in the case of the latter compound the effect was more prolonged (figure 11). In contrast to the marked activity of 9α-fluorohydrocortisone given orally, aldosterone by mouth exerted a definitely less intense electrolyte-regulating effect. It further appeared that, in its sodium-retaining effect, 1 mg. of aldosterone given in four divided doses intramuscularly every six hours was equivalent to 1 mg. of 9α-fluorohydrocortisone given orally as a single daily dose.

It had been previously suggested that aldosterone, the naturally occurring sodium-retaining factor, might not induce excessive sodium chloride retention, in contrast to the effect of a synthetic compound, desoxycorticosterone, employed in the same patients. These earlier studies were carried out with relatively small quantities of aldosterone, i.e., 300 to 400 micrograms per day by injection.[3] To test this hypothesis, a patient with Addison's disease was given 0.25 mg. of aldosterone every six hours for six days. This was associated with marked total sodium and chloride retention, illustrated by a gain of 3.5 Kg. in weight and clinical evidence of excessive accumulation of sodium and water. It was interesting to note that, despite this rather large dose of aldosterone in terms of salt-retaining capacity, little or no organic metabolic-regulating effect was noted, i.e., an increase in the urinary excretion of nitrogen of less than 6% on the first day of aldosterone administration, without an appreciable alteration in the values for uric acid, inorganic phosphorus and true glucose excretion. There was no change in the profile of intravenous glucose tolerance tests and no decrease in melanin pigmentation as measured by skin reflectance spectrophotometry.[18] In a subject with normal adrenal function 1 mg. of aldosterone daily, administered intramuscularly in divided doses, did not suppress spontaneous adrenal cortical secretion. Fluorohydrocortisone and Δ1-fluorohydrocortisone administered by mouth as a single daily dose of 1 mg. did exhibit ACTH-suppressing activity as measured by the urinary excretion of 17-hydroxycorticoids (figure 12).

In the addisonian patient described above, who received 1 mg. of aldo-

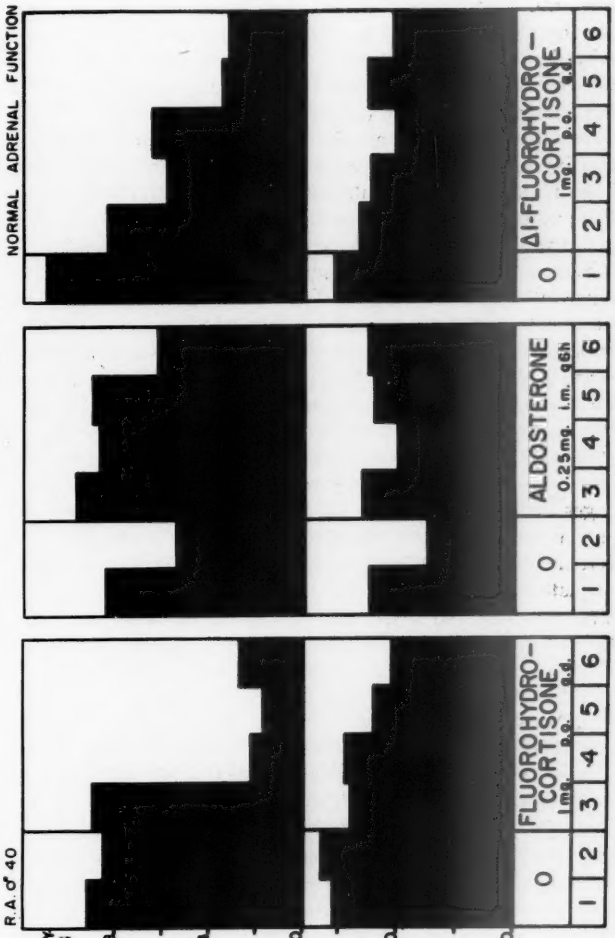

FIG. 12. Effects of fluorohydrocortisone, aldosterone, and Δ1-fluorohydrocortisone on steroid excretion.

sterone daily for six days in divided intramuscular doses, there did appear to be a small but definite decrease in the level of circulating eosinophils in conjunction with aldosterone therapy, the average for the six days being 28% below control levels. The possible significance of the eosinopenia was enhanced by the rebound eosinophilia which was noted following the discontinuance of aldosterone therapy. Three additional patients without functioning adrenal tissue exhibited an eosinopenia of 50 to 60% on 1 mg. of aldosterone given either as an eight hour intravenous infusion or as a single dose by mouth. The discrepancy between the eosinopenic effect observed with aldosterone and its negligible effect on other measurable carbohydrate-regulating mechanisms in general at this dose level raises a question as to whether one might be dealing with a direct eosinopenic action of this substance similar to that observed with epinephrine. This is the first instance in which the authors have observed a marked discrepancy between over-all organic metabolic-regulatory effect of adrenal cortical steroids and their eosinopenic effect. Previous experience indicates that a minimal dose of 35 to 50 mg. of cortisone or hydrocortisone was necessary to produce the same degree of eosinopenia. Thus, in respect to its eosinopenic effect, aldosterone would appear to be 25 to 50 times as active as hydrocortisone, whereas in animal studies concerned with glycogen deposition and a response to cold,[4] and in studies in man relating to organic metabolic changes and pituitary-inhibiting activity, evidence indicates that aldosterone is inferior in activity to hydrocortisone or cortisone. It will be of considerable interest to investigate this phenomenon further when a more nearly adequate supply of aldosterone becomes available. In estimating the ratio of mineralo-corticoid to organo-corticoid activity for aldosterone (figure 4), the specific effect on eosinophils has been disregarded.

Discussion

It would appear from these studies that both substitution of a fluorine atom at the 9α position of hydrocortisone and the introduction of a double bond between carbons 1 and 2 of hydrocortisone result in a markedly increased biologic activity. The potentiation of activity achieved by the substitution of a fluorine atom was considerably greater than that produced by the introduction of the double bond. However, an analysis of the potentiation of sodium-retaining activity on the one hand and of carbohydrate activity on the other hand revealed a marked change in the ratio of these two activities as compared with the ratio prevailing for the parent compound. In the case of the 9α-fluorohydrocortisone, the ratio was shifted toward sodium-retaining activity, whereas in the case of Δ1-hydrocortisone the ratio was shifted toward carbohydrate effectiveness. Since in the majority of instances these steroids are clinically used because of their anti-inflammatory activity, and since anti-inflammatory activity in general

parallels carbohydrate activity, this shift in ratio of activities results in a less favorable therapeutic index for 9α-fluorohydrocortisone and in a more favorable one for Δ1-hydrocortisone. However, it should not be forgotten that in the treatment of chronic inflammatory diseases the early occurrence of salt retention represents at times a warning signal which is noticed by both patient and physician and which often results in a healthy conservatism in the selection of a minimal effective dose. Also, whereas the degree of salt retention encountered in anti-inflammatory therapy with hydrocortisone is as a rule rather easily controlled by salt restriction or by the administration of potassium chloride, the complications which result from gluco-corticoid activity are more insidious in their onset and more serious from a long-range point of view, since they include marked protein depletion, osteoporosis and diabetogenic activity.

While an increase in the gluco-corticoid to mineralo-corticoid ratio results in an improved therapeutic index for the treatment of chronic inflammatory disorders, different ratios may be preferred in different situations. Thus, in the treatment of Addison's disease, where sodium-retaining steroids have to be administered, the shift in ratio toward sodium-retaining activity results in particular usefulness for 9α-fluorohydrocortisone. Furthermore, the ratio of the two biologic activities may at times be of much less importance than the absolute degree of effective potentiation. Thus in all situations where urinary metabolites of the administered steroids are undesirable, the most potent steroid is the steroid of choice. When adrenal cortical steroids are used as substitution therapy during the performance of steroid excretion tests in response to ACTH, to establish or rule out the diagnosis of Addison's disease, 9α-fluorohydrocortisone can be used in dosages of 0.5 to 1 mg. per day. The urinary steroid metabolites from the administered fluorohydrocortisone are then negligible. Similarly, when carbohydrate active steroids are administered in the presence of evident adrenal hyperfunction in order to test whether the adrenal cortical tissue responsible for the hypersecretion of hormone is normally dependent on ACTH stimulation, the most potent gluco-corticoid available will be preferred. The presence of a high degree of salt-retaining activity gives rise to little concern in this instance, since the period of administration will rarely exceed a few days and since excessive salt retention over a short period of time can be prevented.

Finally, it should be stressed that while the ratio of gluco-corticoid to mineralo-corticoid activity has been mainly considered in this study, this is in part due to our inability to assess quantitatively other parameters of steroid activity. It is quite evident that a careful assay of individual biologic effects of each steroid should in time be carried out, and that the most useful compounds may well result from selective potentiation of single activities. It is not easy to predict whether such specific potentiation will in the future become possible.

Summary and Conclusions

The presence of measurable biologic activity in a group of steroid substances related to the adrenal cortical hormones has provided a unique opportunity for correlating change in physiologic function with alteration in chemical configuration. In the present study attention has been devoted to analysis of the over-all effectiveness of substitution of a fluorine atom at the 9α position and of the introduction of a double bond between carbons 1 and 2. These two modifications of hydrocortisone have been of particular interest because of the profound enhancement of biologic activity on the one hand, and significant alteration in the ratio of gluco-corticoid to mineralocorticoid activity on the other (summarized in figure 4). These studies suggest that the continued accumulation of metabolic and chemical correlates will undoubtedly increase the understanding of structure-function relationships and facilitate the selection of further derivatives for which useful metabolic activity can be predicted.

Acknowledgments

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Summario in Interlingua

Synthetic steroides adrenal que possede un activitate biologic plus grande que le productos secretori adrenocortical de occurrentia natural es de alte signification theoric e therapeutic. Le objectivo del presente investigation es comparar le activitate physiologic de 9α-fluorohydrocortisona, Δ_1-hydrocortisona, e Δ_1-fluorohydrocortisona con le activitate physiologic de hydrocortisona e aldosterona. Esseva executate studios in subjectos normal e in patientes con morbo de Addison qui esseva mantenite super un dieta constante. Le hormones esseva administrate intravenose- e/o oralmente. Le sequente factores esseva empleate como indices de activitate physiologic: Alterationes del excretion urinari de natrium e kalium, ver glucosa, nitrogeno e acido uric, alterationes del circulante cellulas eosinophile, e inhibition del endogene secretion adrenal. Studios executate con fluorohydrocortisona pare indicar que le potentia de regulation organic in iste composito es circa 20 vices le potentia correspondente in hydrocortisona. Su potentia de promover le retention de natrium es multo plus grande. In iste respecto 9α-fluorohydrocortisona pare esser tanto potente como aldosterona.

Δ_1-Hydrocortisona monstrava un activitate organicometabolic quatro vices le correspondente activitate de hydrocortisona. Studios de su effecto mineralocorticoide resultava in varie responsas, sed il es possibile asserer que illo ha un definite potentia de retention de natrium e que iste potentia es simile in magnitude al correspondente potentia de hydrocortisona. Studios preliminari con Δ_1-fluorohydrocortisona indicava que le activitate de iste composito es simile al activitate de fluorohydrocortisona.

Le previemente reportate effectos mineral de aldosterona esseva verificate in humanos. Con doses de 1 mg per die nulle significative effecto organicometabolic

esseva notate. Un interessantissime observation esseva que iste substantia ha inter 25 e 50 vices le effecto eosinopenic de hydrocortisona. Isto pare indicar un action directe super le cellulas eosinophile.

Le substitution de un atomo de fluor al position 9α de hydrocortisona, e etiam le insertion de un duple ligamine inter C_1 e C_2, resulta in un marcate augmento del activitate biologic. In le prime del duo casos iste augmento es plus grande. Tamen, si on considera le potentia relative del activitates glucocorticoide e mineralocorticoide in iste substantias in comparation con hydrocortisona, on nota que in 9α-fluorohydrocortisona le proportion se displacia in favor del activitate de retention de natrium durante que in Δ_1-hydrocortisona illo se displacia in favor del activitate organico-metabolic. Per continuar le accumulation de datos in re le correlationes chimic e metabolic in le steroides sub consideration, nos va augmentar nostre comprension del relationes inter structura e function de ille substantias, e isto pote resultar in le synthese selective de nove compositos con desirabile qualitates.

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THE USE OF CORTISONE AND HYDROCORTISONE IN ALLERGY * †

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INTRODUCTION

DURING the last few years compound E (cortisone) and compound F (hydrocortisone) have been used with considerable success to suppress the symptoms of allergic and related disorders. There are those who decry their use, saying that they merely suppress symptoms and that they possess potentially serious side effects. There are also those who seriously misuse these agents, employing them in trivial conditions, often in inadequate dosage and frequently with little or no supervision of the patient. The purpose of this paper is to summarize experiences with cortisone and hydrocortisone in allergic and related disorders during the last four years.

ASTHMA

For simplification, bronchial asthma may be divided into two major categories: one with one or more demonstrable antigen-antibody reactions, and the other with no proved etiology. The age of onset of allergic asthma, the first type, spans from infancy to late life but peaks in late childhood or early adolescence; whereas the onset of asthma of unknown etiology may begin in childhood but generally commences after age 40. Patients with either type of asthma may develop acute paroxysms or have persistent wheezing varying in intensity from mild to severe. Obviously those with mild or moderate symptoms of asthma are not candidates for corticosteroid therapy. Only those with alarming paroxysms or severe persistent symptoms should be considered.

Any patient with asthma may progress to status asthmaticus, which may be defined as a persistent, severe attack of asthmatic symptoms refractory to routine therapy. All such patients should be hospitalized and must receive good nursing care. Adequate fluids should be given. If aminophyl-

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line and epinephrine fail to promise relief after 12 hours, cortisone or hydrocortisone is justified. The use of cortisone in such emergencies has been presented by Burrage and Irwin.[1]

Now that intravenous hydrocortisone is available, it is often suitable to initiate therapy in adults with an intravenous drip of 1,500 ml. of 5% glucose containing 300 mg. of hydrocortisone. This preparation is administered over eight hours and is followed by 50 mg. of oral cortisone or hydrocortisone every six hours until the patient is asymptomatic. In infants and children an intravenous drip of 100 ml. per kilogram of body weight of 5% glucose containing 3 to 5 mg. compound F per kilogram of body weight is given over 24 hours. Then 3 to 5 mg. of cortisone or hydrocortisone per kilogram of weight are given orally in divided doses every 24 hours until recovery. Three points deserve emphasis:

Do not wait until the patient is moribund before starting corticosteroids, for their action is not rapid.

Do not forget the possible value of epinephrine and aminophylline during initial steroid therapy.

Do not anticipate complete remission of symptoms in the first few days.

Once the patient is symptom-free, it is imperative to classify his asthma. No patient with asthma due to demonstrable antigen-antibody reactions should be committed to a long program of daily steroid therapy without deliberation. If the patient's asthma is due to the reaction of a specific pollen and its antibodies, and if sustained asthma is very severe, maintenance therapy for the duration of the present pollen season may be justified. A few patients with asthma of unknown etiology cease to respond to any earlier forms of treatment, and they eventually become social and economic invalids. Maintenance corticosteroid therapy is justified in these unfortunates, most of whom can be restored to normal activity.

Establishment of the daily maintenance dose of cortisone or hydrocortisone is a matter of trial and error. The daily dose is dropped 20 to 25 mg. every two to four days until the patient is off the steroid or until asthma reappears. If maintenance therapy is indicated, the daily dose is raised 10 to 20 mg. above the dose on which symptoms have reappeared. Since the object of maintenance therapy is to obtain complete freedom from symptoms, the daily dose must be high enough to suppress all symptoms of asthma. Experience shows that this daily maintenance dose is stable except during periods of stress or of acute respiratory infections.

Atopic Dermatitis

Atopic dermatitis may be divided into two major groups: infantile eczema, which generally commences at four to six weeks of age and usually clears within the first two years of life, and atopic eczema, which often begins after two years and may continue or reappear at any age. The great majority of patients in both groups can be helped by elimination of respon-

sible antigens and by simple topical therapy. Fortunately, atopic dermatitis in most patients does not run a sustained course, and corticosteroid treatment is therefore rarely indicated.

In a few patients the dermatitis is most resistant. An etiologic diagnosis cannot be made. Usual therapy fails to such an extent that manifestations of eczema in infants and children disrupt the home and, in adults result in loss of economic and social status. After thorough study such patients may be considered for cortisone or hydrocortisone.

Topical application of these steroids is frequently effective. Ointments containing cortisone have been abandoned because cortisone has proved less effective than other steroids when applied locally. Hydrocortisone (2.5% ointment) as well as 9 alpha fluorohydrocortisone (0.1% and 0.2% ointments) often suppress symptoms to such a degree that the skin improves or clears. Such ointments should be applied to involved areas at least every eight hours. Once these ointments are stopped in these resistant cases, symptoms usually return promptly. The big advantage of local therapy has been the lack of side effects. Sulzberger and associates [2] found hydrocortisone ointment of marked benefit in 20 of 30 patients with atopic dermatitis, and noted no side reactions and no evidence of contact sensitization during eight months of continuous therapy. Since resistant eczema must be treated almost endlessly, continued use of these various steroid ointments may well lead to side effects in the future.

When local therapy is not effective, or when active lesions are extensive, systemic cortisone or hydrocortisone may be used. Dosage schedules are similar to those described under asthma for both children and adults. Just how long such daily maintenance therapy is justified remains to be determined. Hill [3] maintained a group of patients with eczema on daily oral cortisone for many months without many severe side effects. Repeated attempts to lower daily dose and to withdraw patients from these hormones are indicated, because long-term steroid therapy may well show side effects at a later date.

Contact Dermatitis

Contact dermatitis is due to various sensitizing agents, which include plant oils, resins, dyes, metals and their salts, turpentine, pyrethrum, cosmetics, adhesive tape, plastics, paints, and drugs such as tar, iodides, mercury, sulfur, quinine, sulfonamides, antibiotics and procaine. Almost any agent may be responsible. Treatment consists of finding the responsible agent or agents and removing the patient from contact with them. Symptomatic treatment is indicated for relief of existing lesions. Simple measures often suffice.

In severe, generalized cases of contact dermatitis a short course of compound E or F may be indicated. A few may be so ill as to be unable to retain oral medication, and in such individuals an initial course of intravenous compound F as described under asthma is indicated. This may be followed

by oral cortisone or hydrocortisone until symptoms clear. In adults 50 mg. of either cortisone or hydrocortisone are given every six hours until the skin is almost clear. The dose is then reduced daily in steplike fashion until the patient is off therapy. There are some patients with marked involvement of only one or two areas. Here topical application of a lotion 0.2% 9 alpha fluorohydrocortisone every eight hours has proved to be an aid.

Drug and Serum Reactions

The emphasis in treatment of serum sickness and drug reactions should be placed on prevention. If physicians would immunize their patients against diphtheria and tetanus with toxoids and give booster injections as needed, serum sickness would be a rare occurrence. Drug reactions could be drastically reduced if patients and doctors were alerted to minor unusual symptoms produced by medication. Many reactions due to drugs would be avoided if physicians prescribed antibiotics only when they are clearly indicated, rather than just to "do something for the patient."

Cortisone and hydrocortisone have little place in the treatment of serum sickness. Symptoms usually clear within a reasonable period of time. If symptoms are persistent and severe, a short course of either hormone may be useful. The dosage schedule described under asthma is adequate.

Drug reactions vary. When the response is anaphylactoid in type, as in the patient described by Irwin and associates,[4] corticosteroids would be of no value because either death or recovery would occur before they could be effective. When the reactions are mild, with only urticaria or mild dermatitis, cortisone and hydrocortisone should not be used. Drugs can cause persistent fever, massive angioneurotic edema, swelling of laryngeal mucosa, marked arthritis, asthmatic symptoms and exfoliative dermatitis. In such instances cortisone or hydrocortisone should be used. Shulman and associates,[5] the Friedlaenders[6] and Feinberg and associates[7] have all reported success. Satisfactory results depend upon adequate dosage.

Nasal Allergy

Nasal allergy might be divided into seasonal hay fever and vasomotor rhinitis. Oral cortisone and hydrocortisone should not be employed in seasonal hay fever, even though both will suppress symptoms, as reported by Schiller and Lowell.[8] Here the symptoms are not serious and usually can be adequately handled by other methods. Corticosteroid therapy is not recommended in the treatment of vasomotor rhinitis.

Nose drops containing 15 mg. of compound F/ml. or 5 mg. of 9 alpha fluorohydrocortisone/ml. have recently become available. Initial experience with these agents over short periods of time in both hay fever and vasomotor rhinitis suggests that they do suppress symptoms. Whether these preparations will lead to side effects remains to be determined. Symptoms do re-

turn promptly once nose drops are stopped. In general, nose drops are not satisfactory agents to use for long periods in treatment of nasal allergy.

Urticaria and Angioneurotic Edema

Urticaria and angioneurotic edema can be troublesome but are rarely dangerous. In about one third of the patients, specific antigen-antibody reactions can be demonstrated. Fortunately, attacks generally clear spontaneously. If the responsible antigens are found, elimination solves the problem.

Corticosteroids have little or no place in the therapy of these disorders. Persistent lesions due to drugs or serum have been discussed under that section. Patients are rarely encountered with frequent attacks of laryngeal swelling of such magnitude that life is threatened. In one such patient, epinephrine was not effective and frequent emergency tracheotomies were necessary. Etiology was not determined in spite of repeated efforts. Three short courses of cortisone broke the vicious cycle.

Blood Diseases

Hematologists have suspected that many cases of idiopathic thrombocytopenic purpura, anaphylactoid (Henoch-Schönlein) purpura, acquired hemolytic anemia, erythroblastosis fetalis, hypoplastic or aplastic anemia, leukopenia and agranulocytosis might well be based on antigen-antibody reactions. Recently Ackroyd [9] demonstrated that the platelets of normal individuals agglutinated on the addition of Sedormid and the serum from patients with thrombocytopenic purpura thought to be due to Sedormid. The Coombs' test,[10] which is positive when the red cells of a patient with erythroblastosis fetalis or acquired hemolytic anemia are clumped upon the addition of rabbit's antihuman globulin serum, supports in part the hypothesis that these diseases depend upon an immunologic reaction.

Cortisone and hydrocortisone have been used in all these blood disorders. The literature is voluminous, and in cases of each type, success, partial success and failure have been reported. Final evaluation depends on further observations.

Collagen Diseases

Rheumatoid arthritis, polyarteritis nodosa, rheumatic fever, disseminated lupus erythematosus, generalized scleroderma and dermatomyositis are characterized by extensive damage to connective tissue. At one time or another the possibility has been suggested that each of these disorders is based on immunologic reactions. Rich and Gregory [11] injected foreign protein at stated intervals into rabbits and produced lesions similar to those of periarteritis nodosa. To date, this is the best evidence to support such hypotheses.

Physicians interested in arthritis and rheumatic fever are evaluating cortisone and hydrocortisone in these two diseases.

Since the courses of polyarteritis nodosa, disseminated lupus erythematosus, systemic scleroderma and dermatomyositis generally are unfavorable, an adequate trial of cortisone or hydrocortisone may well be justified. Again an honest attempt to control symptoms must be made, and it may be necessary to use 500 mg. to 1 gm. of either hormone daily for a short period in order to suppress symptoms adequately.

Contraindications

Before a decision is made to prescribe compound E or F, consideration of certain contraindications is imperative. Kass and Finland's review [12] showed that corticotropin or cortisone can increase the virulence and mask the manifestations of many infections and that they can activate latent infections. Spread and activation of tuberculosis [13, 14] have been reported.

Table 1

Name	Sex	Age	Duration of Steroid Therapy Before Complication	Daily Average Dose of Steroid	Complication
F. G.	F	47	640 days cortisone 151 days hydrocortisone	95 mg. 80 mg.	Osteoporosis with compressed vertebral fractures
A. E.	F	73	865 days cortisone	50 mg.	Osteoporosis with compressed vertebral fractures
P. B.	M	72	880 days cortisone 268 days hydrocortisone	70 mg. 50 mg.	Osteoporosis with compressed vertebral fractures
B. B.	F	52	65 days hydrocortisone	150 mg.	Osteoporosis with compressed vertebral fractures
W. G.	M	61	240 days cortisone	100 mg.	Osteoporosis with compressed vertebral fractures
			480 days cortisone	100 mg.	Bleeding duodenal ulcer Masked pneumonia

Recent articles [15, 16, 17] suggest that ACTH and corticosteroid therapy can be used in the presence of active tuberculosis, provided adequate antibiotic therapy is also given. Nevertheless, it would seem best to avoid these hormones in the presence of tuberculosis and of other serious infections until more is known.

Gastrointestinal bleeding [18] has been reported in patients receiving corticotropin and steroids. Patients with peptic ulcer, ulcerative colitis and regional ileitis probably are not good risks for such treatment. If such patients are given compounds E or F for severe allergic or related disorders, they require the closest supervision.

Reports [19, 20] of psychoses and osteoporosis complicating steroid therapy suggest that patients with these disorders or with a suggestive history are poor risks. Postmenopausal women in whom the removal of the uterus and

both ovaries has led to an artificial menopause are prime candidates for osteoporosis. Such women should be kept off corticosteroids even if roentgenograms of their vertebrae show little evidence of this disorder.

Complications

Some complications can easily be ascribed to therapy, whereas others are more difficult to explain. Patients on relatively short courses of these hormones generally do not develop untoward symptoms, but with maintenance therapy complications have been noted. For the past four years about 30 adults with severe, intractable asthma of unknown etiology have been maintained symptom-free on daily doses of compound E or F for periods ranging from one to four years.

All of these patients have shown facial rubor, rounding of facial contours, weight gain and abnormal distribution of weight, with increased fat in abdominal, facial, supraclavicular and lower cervical areas. Most of the female patients have an increased amount of facial hair. Two male patients developed acne. Serious problems have appeared in three of these patients and in two others seen after onset of complications. Table 1 lists these patients.

Since W. G. suffered from no less than three complications possibly related to cortisone, his case is reported in detail.

Case Report

Asthma first appeared in this man at age 36 in September, 1928, and became intractable. Rarely was he free from symptoms. All attempts to establish an etiologic diagnosis failed. During the first 23 years of asthma he saw many doctors and spent much time in various hospitals, including six admissions to the Massachusetts General Hospital. He was hyposensitized to ragweed, dust and alternaria, without benefit. He received courses of bacterial vaccines; he tried aminophylline, ephedrine, epinephrine, oxygen, chloral hydrate, expectorants, barbiturates, and various combinations of these medicaments. Each year found him worse. Within two years of onset he was unable to carry on as a skilled machinist. By September, 1951, he was reduced to being a steward in a small yacht club, and could keep this job only because his wife and his son performed the greater part of his duties. Most of his time was spent propped up in bed. To add to his misery, a duodenal ulcer appeared in 1946. Fortunately, this responded to medical therapy. By 1950 he had developed osteoporosis and kyphosis with one compressed vertebra.

On September 15, 1951, he was admitted to the Massachusetts General Hospital in "status asthmaticus." Routine antiasthmatic therapy, including good nursing care, did not suffice, and so cortisone was started September 27, 1951. He responded well, and on October 10, 1951, was discharged symptom-free on a daily dose of 100 mg. of cortisone. Because of the history of duodenal ulcer and because osteoporosis was present, cortisone was gradually withdrawn. November 1, 1951, found him off steroid therapy, but once again his asthma became severe. During the following nine months he remained an asthmatic invalid and spent 60 days in the hospital. On August 28, 1952, "status asthmaticus" required his readmission to the Massachusetts General Hospital, where his life was threatened when routine treatment did not help. On August 29 he was again placed on cortisone. He responded well. The risk of main-

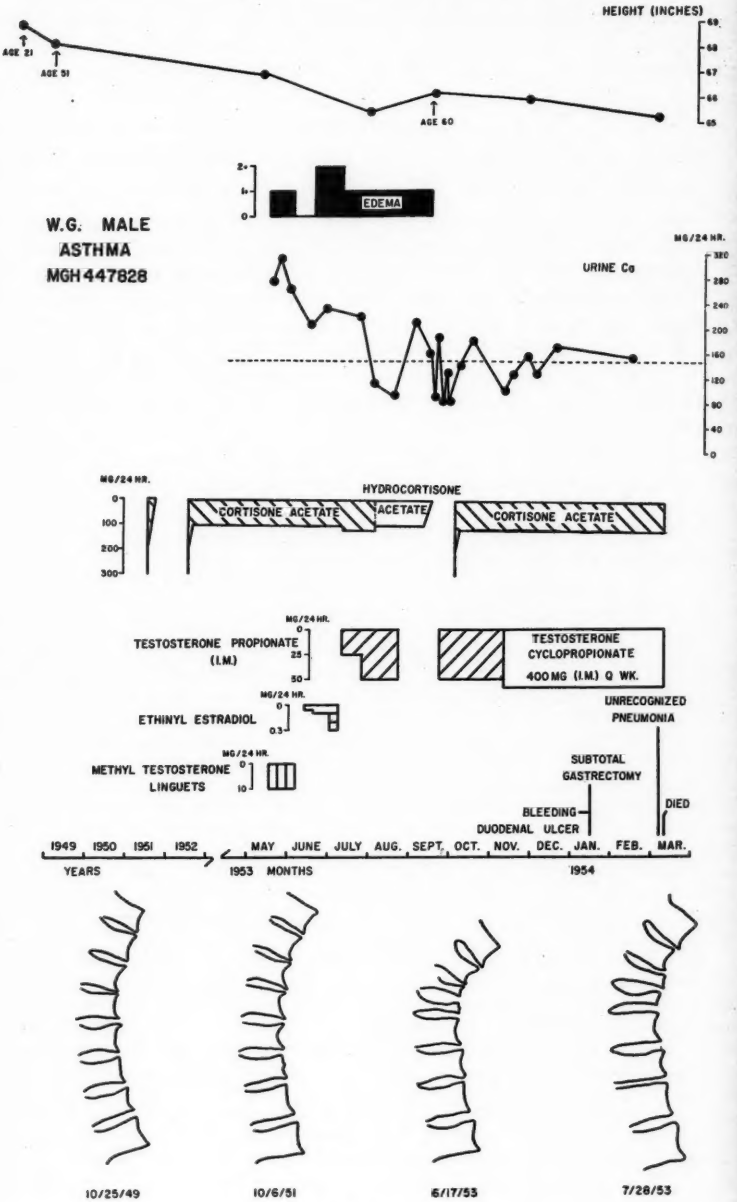
HEIGHT (INCHES)
AGE 21
AGE 51
AGE 60
EDEMA
W.G. MALE
ASTHMA
MGH 447828
URINE Co
MG/24 HR.
HYDROCORTISONE
CORTISONE ACETATE
ACETATE
CORTISONE ACETATE
TESTOSTERONE PROPIONATE (I.M.)
TESTOSTERONE CYCLOPROPIONATE 400 MG (I.M.) Q WK.
ETHINYL ESTRADIOL
METHYL TESTOSTERONE LINGUETS
UNRECOGNIZED PNEUMONIA
SUBTOTAL GASTRECTOMY
BLEEDING DUODENAL ULCER
DIED
1949 1950 1951 1952 MAY JUNE JULY AUG. SEPT. OCT. NOV. DEC. JAN. FEB. MAR.
YEARS
1953 MONTHS
1954
10/25/49
10/6/51
6/17/53
7/28/53

FIG. 1.

tenance steroid therapy in a man with a peptic ulcer history and with existing osteoporosis was grave, but life held little for this man if his asthmatic symptoms were not controlled.

Figure 1 charts his course. His daily maintenance level of cortisone proved to be 100 mg. He did well for eight months, until April 30, 1953, when he developed back pain. Roentgenograms of his vertebrae showed compression fractures of his thoracic vertebrae. Urinary excretion of calcium was markedly increased, as charted in figure 1. The dilemma which presented itself was whether to stop cortisone, with the likelihood that cough and wheeze would recur, thereby aggravating the spinal pain, or to continue with cortisone and risk rapid progression of the osteoporosis.

It was decided to go ahead with cortisone but to attempt to control the osteoporosis with estrogen or testosterone. Figure 1 demonstrates that methyl testosterone linguets did not effectively reduce his urinary calcium excretion. In addition, he developed peripheral edema, which disappeared when the testosterone was discontinued. Ethinyl estradiol was tried. Once again edema appeared, this time to such an extent that he was unable to put on his shoes. His 24-hour excretion of calcium, however, did fall. On June 12, 1953, ethinyl estradiol was stopped. The edema decreased. Testosterone propionate, 25 mg. intramuscularly daily, was substituted on July 17, 1953. The edema increased, but the 24-hour urine calcium dropped. While he was in the hospital between September 16, 1953, and September 25, 1953, both cortisone and testosterone were withdrawn. His edema cleared, but during the first three days off cortisone he suffered headache, nausea, loss of appetite and weakness. On September 24 he was started again on testosterone propionate, 50 mg. intramuscularly daily. Recurrence of severe asthma necessitated return to cortisone on October 5. Edema was no longer a problem. In November he was switched from testosterone propionate to 400 mg. testosterone cyclopropionate intramuscularly at weekly intervals. Edema did not reappear.

On January 14, 1954, he developed a bleeding duodenal ulcer which did not respond to medical treatment. A subtotal gastrectomy on January 15 was uneventful. Preceding and following surgery he received increased amounts of cortisone. Wound healing seemed to progress well. Just before discharge on January 29, however, he argued about his medication with his nurse. "Something stuck" in his throat, which led to coughing and, in turn, to the opening of his incision. The wound was closed in the operating room after an emergency tracheotomy, necessitated by laryngospasm during induction of anesthesia. He did well and returned home February 7.

Satisfactory progress was made until March 8, 1954, when at 2 p.m. he felt weak and tired. Back pain became severe. He was seen at home by one of us on March 9. The lungs were clear, the pulse was weak but regular, the blood pressure was 110/80 mm. of Hg, and the temperature, 98.4° F. The patient refused to return to the hospital. He was placed on KCl tablets, 1 gm. every six hours. At 8:30 a.m. on March 10 he died suddenly while at stool.

Autopsy

The autopsy was performed six and one-half hours after death. The body was that of a well preserved, well nourished man. The surgical incisions were well healed.

The right lung weighed 1,300 gm., the left 600 gm. The lower half of the right upper lobe, most of the right middle lobe, and parts of the right lower lobe were consolidated and covered by fine, fibrinous adhesions. The right pleural cavity contained 500 ml. of straw-colored fluid. Microscopic examination showed that the alveoli in the consolidated areas were filled with neutrophils. Fibrin was inconspicuous. The alveolar walls were intact, with markedly engorged capillaries. The bronchioles were filled with neutrophils, but retained their epithelium. Emphysema

TABLE 2

Cell Type	Relative Percentage Patient W. G.	Normal Men Over 50 (Mellgren)
Basophils	10.5	12.2
Hyaline basophils	3.5	0.05
Acidophils	29.8	31.7
Amphophils	20.2	4.5
Hypertrophic amphophils	1.8	0.30
Chromophobes	34.2	51.3

was marked only in the upper parts of the upper lobes, where there were large blebs and moderate fibrosis of the alveolar wall. Some of the medium sized bronchi had thickened basement membranes, but many did not. Muscular hypertrophy was not evident. The epithelium of the bronchi was unremarkable. There were no mucus plugs. Cultures from the right middle lobe grew a few pneumococci and a moderate number of *Escherichia coli*.

The heart weighed 450 gm. There were many petechiae in the epicardium. The myocardium of the right ventricular wall was thickened to 8 mm., that of the left ventricular wall to 18 mm. Microscopic examination of sections stained with hematoxylin and eosin or phosphotungstic acid hematoxylin revealed only a few small foci of myocardial fibrosis. Sections stained by the periodic acid-Schiff method showed occasional muscle fibers in which there was a sharply defined, central, PAS-positive area which was always smaller than the cross section of the fiber and extended along

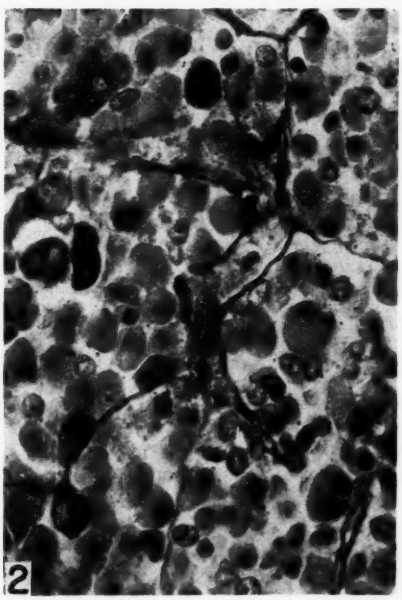

FIG. 2. Hypophysis of 19 year old man with normal endocrine glands and sudden death from cerebrovascular accident. The black cells are basophils and the large gray cells acidophils. Periodic acid Schiff-Orange G stain.

it for not more than one or two times its diameter. These sharply defined areas were unlike the ill-defined zone of PAS-positive staining seen in the ends of muscle fibers interrupted by a focus of fibrosis. The myocardia of several cases without evidence of hypokalemia or myocardial abnormality were stained by the periodic acid-Schiff method as controls. In some, occasional muscle fibers showed exactly similar, sharply defined, central PAS-positive areas, and in most there was ill-defined PAS-positive staining of the ends of muscle fibers interrupted by fibrosis.

The pituitary weighed 300 mg. (normal, approximately 500 mg.). A differential count was performed on 3,079 cells from 71 fields of two sections prepared by the periodic acid-Schiff technic with an Orange G counterstain. This method differentiates three types of chromophil cells: intensely Schiff-positive, well granulated

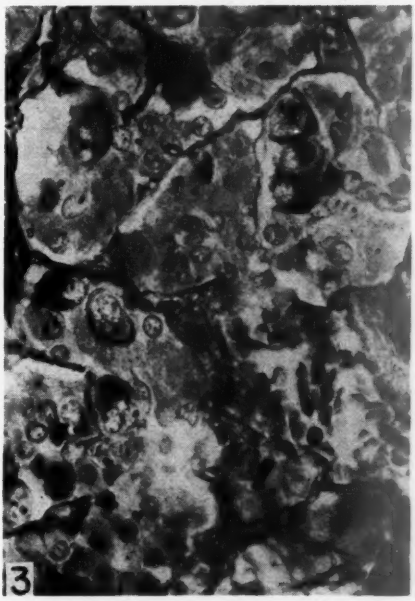

FIG. 3. Hypophysis of patient W. G. Note Crooke's hyaline change in the basophils. The cells with large vesicular nuclei, prominent nucleoli and abundant pale gray cytoplasm are amphophils. Periodic acid Schiff-Orange G stain.

basophils, well granulated Schiff-negative acidophils, and a third type, a sparsely granulated, weakly Schiff-positive cell which has been called an "amphophil," [21] "sparsely granulated basophil" [22] or "intermediate mucoid cell." [23] Basophils and acidophils were within normal limits, but amphophils and hypertrophic amphophils were unusually abundant, and Crooke's hyaline basophils, which have been previously described in spontaneous Cushing's disease,[24] were seen (table 2). Figure 2 shows a section from a normal pituitary, and figure 3 shows a section of W. G.'s pituitary.

Both adrenals were small. The right adrenal weighed 4.2 gm., the left, 3.8 gm. Microscopic examination showed that the cortices were thinned. The cortical cells were all vacuolated, and nuclei tended to be pyknotic. Tubular change was

occasionally present.[25] Congestion was sometimes marked, especially at the corticomedullary junction. Figure 4 shows a section of a normal adrenal, and figure 5 shows a section of W. G.'s adrenal.

The testes weighed 18 gm. each. There was moderate peritubular fibrosis. Leydig's cells were few. Spermatogenesis was rarely evident, most tubules containing only vacuolated Sertoli's cells. The thyroid, parathyroid, thymic and pancreatic glands were unremarkable.

The kidneys weighed 160 gm. each. Microscopic examination showed only a few small foci of subcapsular fibrosis. The tubules were slightly dilated, but their epithelium was intact and without vacuolar change. The distal part of the stomach had been removed surgically, but the gastrojejunostomy seemed to be functioning

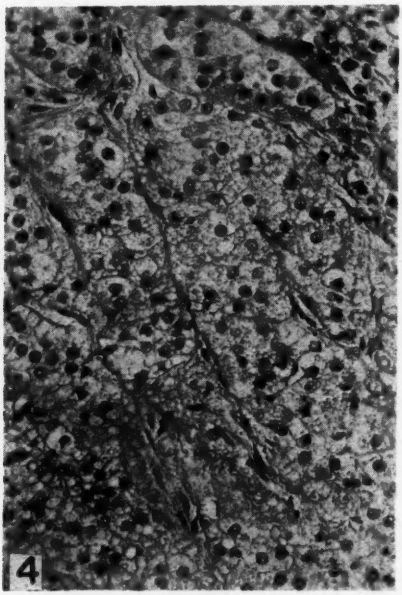

FIG. 4. Adrenal cortex of endocrinologically normal 19 year old man. Note vesicular nuclei and fine lipoid droplets in cytoplasm. H. & E.

well. The anastomoses were well healed. The gall-bladder contained many mixed stones of cholesterol and bilirubinate. The spleen contained small foci of hemorrhage into the pulp. Three of the four enteric-coated tablets of potassium chloride given by mouth were recovered intact from the terminal ileum or colon. Search was not made for the fourth tablet.

There were compression fractures of the fifth, sixth and seventh thoracic vertebrae and healed fractures of the left seventh and eighth ribs. Osteoporosis was marked. The bodies of the vertebrae were soft, and the ribs were brittle. Microscopic examination showed that in the medulla bony trabeculae were few and thin, and were scattered through a fatty hematopoietic marrow. There was no evidence of osteoid and little osteoblastic or osteoclastic activity. Hematopoiesis was

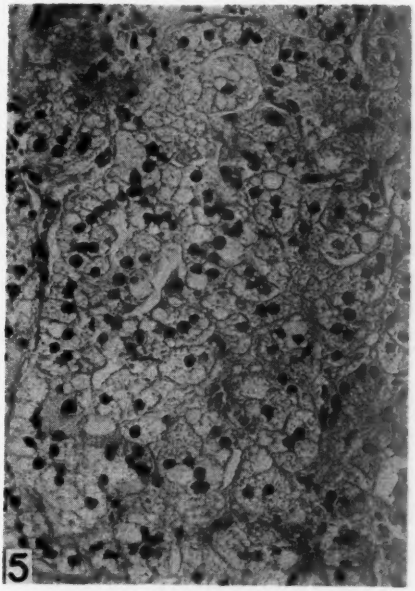

FIG. 5. Adrenal cortex of patient W. G. Note pyknotic nuclei and coarse lipoid droplets in cytoplasm. H. & E.

proceeding normally. The fractures in the ribs were repaired by large quantities of poorly ossified cartilage. Except for an occasional small zone of fibrosis near an intervertebral disc, there was no sign of repair in the compressed vertebrae.

Pathologic diagnoses included: severe bronchopneumonia; severe pulmonary edema; pulmonary emphysema; right hydrothorax; bilateral pleural adhesions; severe osteoporosis; compression fractures, fifth, sixth, seventh, thoracic vertebrae; healed fractures, seventh and eighth ribs; cardiomegaly (predominantly right ventricular); adrenal atrophy; testicular atrophy; cholelithiasis; operations: partial gastrectomy and tracheotomy, healed.

DISCUSSION OF CASE

This man had suffered from severe, uncontrolled asthma of unknown etiology from his twenty-eighth year. Therapy was of little avail until at the age of 60, when he was rendered symptom-free with cortisone. Maintenance cortisone kept him free from symptoms for eight months, when compression fractures of the spine again rendered him an invalid. Osteoporosis, which had been evident before cortisone was started, had grown worse during steroid therapy. Estrogen and testosterone did not reverse the bony damage. A duodenal ulcer, known to have been present before the beginning of cortisone therapy, bled during this treatment, but a gastrectomy was successful. On March 8, 1954, after a few days of acute illness, he died unexpectedly.

Autopsy showed the immediate cause of death to be an extensive bronchopneumonia. Much of the right lung was consolidated, with marked edema and occasional foci of very early pneumonia elsewhere in the lungs. The histologic appearance of the pneumonia is consistent with an onset some two days before death, as suggested by the history.

There have been several reports of death from pneumonia in patients on ACTH or adrenocortical steroids, and in at least three cases the pneumonia was not suspected clinically.[26, 27, 28] It is known that cortisone can suppress the symptoms of pneumonia and other infections.[28, 29] It is also known that cortisone and ACTH reduce the body's resistance to many experimental infections, including those with pneumococci.[12, 30] It must be assumed that in the case of W. G. the cortisone suppressed the symptoms of pneumonia almost completely, thus depriving him of the possible benefits of antibacterial therapy. Whether the cortisone also lowered his resistance to the infection cannot be decided on the evidence available. The rapidity of the death in this and the two cases reported by Page [28] does suggest that hormone therapy may lower the body's resistance. Of the various ways in which cortisone might depress the body's resistance to infection,[31] it can only be said that in the case of W. G. there was no evidence that the inflammatory reaction had been altered in any way.

It is of interest that the lungs did not show to any marked degree the histologic changes described in cases of severe asthma. Some bronchioles did have thickened basement membranes, but the change was not outstanding. Muscular hypertrophy was not seen in the lung, nor were mucus plugs found. Whether the prolonged cortisone therapy played any part in preventing these morphologic changes cannot be decided on the evidence at hand.

As it is known that cortisone therapy can sometimes cause hypokalemia, and as it has been reported that the potassium level may fall so low as to cause symptoms, particular search was made for evidence of hypokalemia in this case. In certain cases of chronic diarrhea, prominent vacuolation of the epithelium of the proximal convoluted renal tubules has been reported.[32] It has been suggested that this vacuolation may be due to hypokalemia,[33, 34] though it should be remembered that the lesion is unlike the tubular change described in experimental hypokalemia.[35–37] No such vacuoles were found in W. G. Sections of myocardium were stained by the periodic acid-Schiff sequence in the hope that this method would reveal early myocardial abnormalities such as might be caused by hypokalemia.[38] The stain did reveal abnormalities, but none which were not also found in control cases.

Bennett [38] discusses the changes found in the adrenal and pituitary glands of patients treated with cortisone. In the adrenal glands the outstanding features were low weight, narrowing and pallor of the cortex, and loss of lipid. In W. G., the glands were a little lighter than normal and the

cortices were thinned, but the cortical cells were well vacuolated. Congestion was marked at the corticomedullary junction. Tubular change was present but was not marked. It may be relevant that Wilbur and Rich [39] have reported that adrenal tubular change can be produced in the rat by large doses of ACTH.

An increase in the amphophils and hypertrophic amphophils of the pituitary has been previously reported in adrenal insufficiency. These cells appear to be the source of several hormones, and are suppressed by large amounts of cortisone.[21] The presence of abnormally abundant amphophils in the pituitary of patient W. G. would therefore suggest that, although the cortisone he received terminally was sufficient to control his asthma, it was not sufficient to suppress a somewhat unusual degree of pituitary activity. Several other workers have reported Crooke's cells in the pituitaries of patients receiving cortisone, and an increase in normal basophils may also sometimes occur.[40, 41]

Osteoporosis and compression fractures of the vertebrae have been reported in cases on cortisone or corticotropin therapy.[20] In this case the bony trabeculae were very few, and there was no osteoid or other evidence of repair. It is evident that the androgen and estrogen therapy administered had not been demonstrably effective.

Conclusions

Cortisone and hydrocortisone are useful therapeutic agents in selected cases of allergic and related disorders. It is true that these steroids possess potentially dangerous side effects. It is also true that long-term maintenance therapy has proved more dangerous than short-term treatment. It has become fashionable to condemn the use of cortisone and hydrocortisone, but it may be necessary to employ these steroids if other therapy proves unavailing.

It is recommended that each patient with severe allergic and related disease be studied with care before being placed upon corticosteroid therapy. Such treatment is often far easier to initiate than to terminate. If cortisone and hydrocortisone are to be used, the patient should also be taken into the physician's confidence and should be made aware of the drawbacks as well as the advantages of steroid therapy.

If long-term maintenance therapy is necessary, the doctor and patient must coöperate throughout treatment. The patient should be seen at frequent intervals and examined thoroughly. He must likewise be instructed to report all deviations from normal. At the same time, all possible means of protecting the patient from undesirable side effects must be explored. The steroid chemists are searching for effective and safer compounds. New compounds are rapidly becoming available, but only time and careful clinical evaluation of each will determine its true worth.

Last but not least, the search for the modes of action of these adreno-

cortical steroids must be continued and encouraged. Success in this field of investigation may ultimately lead to safer use of these agents, and perhaps will even bring about a better understanding of allergic and related diseases.

Summary

1. Indications, contraindications, methods and complications of cortisone and hydrocortisone in the treatment of allergic and related diseases are discussed.

2. One case report with autopsy findings illustrates several of the problems encountered during maintenance corticosteroid therapy.

Summario in Interlingua

Es describite le uso de cortisona e hydrocortisona in asthma, dermatitis atopic, dermatitis a contacto, reactiones medicamentose e seral, allergia nasal, urticaria, angio-edema, e altere disordines allergic. Indicationes, contra-indicationes, e complicationes es discutite in grande lineas. Es presentate programmas medicational pro le controlo initial del symptomas e etiam pro le suppression prolongate del symptomas.

Inter le grave complicationes nos mentiona comprimite fracturas de vertebras, sanguinante ulceres peptic, e infectiones mascate. Iste typo de complication esseva incontrate solmente post therapias mantenential de longe durantia. Nos lista omne negative effectos lateral que nos ha observate.

Il habeva in nostre experientia un caso mortal. Le patiente in question habeva essite mantenite super un regime con doses diurne de cortisona durante un periodo de duo annos. Iste regime habeva como objectivo le suppression de symptomas asthmatic que esseva sever e refractori a omne therapias altere que un therapia a steroides adrenocortical. Post 240 dies del curso de cortisona, iste patiente disveloppava comprimite fracturas de plure vertebras. Un sanguinante ulcere duodenal se manifestava post 480 dies del curso de cortisona. Le osteoporosis esseva combattite per medio de testosterona. Pro controlar le sanguination, un gastrectomia subtotal esseva executate. Non-recognoscite pneumonia precipitava finalmente le exito mortal. Le autopsia revelava un extense bronchopneumonia. Le cortices del glandulas adrenal esseva tenue, e cellulas adrenocortical esseva vacuolate. Cellulas de Crooke esseva presente in le glandula pituitari, e le numero del cellulas amphophile esseva augmentate. Nulle processo reparatori esseva manifeste in le fracturate vertebras.

Cortisona e hydrocortisona es utile agentes therapeutic in seligite casos de disordines allergic e affin, sed illos non pote reimplaciar le establite procedimentos e therapias. Cata patiente individual representa un problema individual, e regulas general non merita nostre confidentia si nos desira succeder. Le hormones in question possede, sin dubita, le potential de grave reactiones lateral, e isto significa que un meticulose surveliantia de omne patiente es indispensabile. Le successo final depende del cooperation inter medico e patiente.

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HEPATITIS IN MONONUCLEOSIS *

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KNOWLEDGE that infectious mononucleosis affects many organs, and publication of increasing numbers of articles dealing with complications, may engender a tendency to overestimate the incidence of complications and the gravity of the uncomplicated disease.

The observations to be presented, as well as observations of others,[1] indicate that liver involvement is not a complication but a regularly occurring feature of mononucleosis. This is not surprising, since the cause of mononucleosis appears to stimulate proliferation of lymphocytes, and the mesenchymal cells of the liver are potential precursors of lymphocytes. The realization that acute hepatitis is regularly present may be followed by the unwarranted assumption that this acute viral hepatitis should be managed like other viral diseases of the liver. Indeed, this recommendation has already been made.[1c] However, it is not logical to recommend identical therapeutic regimens for two viral diseases merely because they affect the same organ.

The primary purpose of this investigation was to ascertain whether histologic studies would support or controvert the belief, based on clinical experience,[2] that the hepatitis of mononucleosis is mild, and that therefore early ambulation is unlikely to be harmful. The secondary purpose of the investigation was to add to the published reports of needle biopsies in mononucleosis, since these reports are not plentiful and few deal with as many patients as we have studied. Incidentally, the clinical manifestations and the histopathology were compared with observations in "infectious hepatitis."

Lymphocytic infiltration of many organs has been described in autopsy reports of cases of mononucleosis.[3] Most of the authors of these reports agree [4] that the outstanding change seen in the liver is the presence of many mononuclear cells in the portal areas and throughout the lobules within sinuses. Neutrophils are practically absent, and evidence of liver cell damage is minimal.

Since autopsy reports are likely to represent unusually severe cases, rather than the most commonly seen or "average" cases, and since the histology of a liver specimen obtained at autopsy may be somewhat distorted by postmortem changes, needle liver biopsies were performed to investigate the degree of hepatic damage in a succession of seven unselected patients with mononucleosis. Liver biopsies were also performed on three mononucleosis patients with jaundice to compare the hepatic histopathology of such

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From a United States Army Hospital.

patients with that of nonjaundiced patients. Also, a comparison with the hepatic pathology of "infectious hepatitis" was important because patients with the latter disease have been managed with utmost conservatism, in the belief that prolonged bed-rest will prevent residual damage and hasten, and tend to insure, complete recovery.

Clinical Observations

In the report of mononucleosis concerning cadets at the United States Military Academy,[2] it was pointed out that disability, fatigue or other symptoms were unlikely to persist after discharge from the hospital in this group of unusually well motivated young men. Within a few days after becoming afebrile, most of these patients returned to academic activities; and

Table 1

Patient.....	1	2	3	4	5	6	7	8*	9*	10*
Days ill	9	8	13	22	16	8	12	13	20	12
Day (after onset of illness) biopsy was performed	8	18	17	19	14§	20	12	45	21	18
Serum bilirubin†	0.2	0.4	0.2	0.4	0.4	0.7	0.5	0.7	1.1	0.9
Highest serum bilirubin and day of illness	0.5 18th	0.4 17th	0.2 17th	0.5 9th	0.4 13th	1.4 7th	0.8 15th	8.0 6th	2.7 15th	3.3 10th
BSP retention†	15%	15%	1%	2%	2%	11%	—	—	5%	17%
Cephalin flocculation‡	4+	3+	4+	4+	4+	4+	3+	4+	4+	3+
Thymol turbidity‡	7.5	—	—	—	—	10.0	11.5	6.5	9.5	11.0

* These patients were jaundiced.
† These tests were performed at time of biopsy or within 24 hours.
‡ Highest values during course of illness.
§ A second biopsy performed 34 days after onset of illness.

after attending classes for several days, they were given specially devised physical reconditioning exercises. One to two weeks later they resumed the regular, physically exacting duties of cadet life. All of these 69 patients were seen in follow-up visits for at least three months, and most of them were followed for one or more years. No undesirable effects of early return to duty were seen. During the ensuing years we have continued to release mononucleosis patients from the hospital shortly after symptoms disappeared, and we have seen no ill effects.

Bender [5] and Hoagland and Gill [6] have emphasized that reports of mononucleosis should be confined to cases meeting all three prerequisites for diagnosis: clinical, hematologic and serologic. All of the liver biopsies described herein were performed on patients who met these requirements, including significant titer of the heterophil reaction of serum after guinea

pig kidney absorption. All except one had heterophil agglutination titers, after absorption with guinea pig kidney, of at least 1:112. One patient had a heterophil titer, unabsorbed, of 1:28 on the sixth day of illness. It rose to 1:56 (and to 1:28 after guinea pig kidney absorption) on the eleventh day of illness, and remained thus on the nineteenth day.

Unlike the typical patient with infectious hepatitis, who seeks medical attention because of yellow sclerae, the typical patient with mononucleosis seeks medical attention because of fever, chilliness, malaise and, usually, sore throat. Patients with mononucleosis are infrequently jaundiced when first seen by a physician.

Probably only 5% of patients with mononucleosis appear jaundiced at any time. We noted jaundice in only four of 100 consecutive mononucleosis cases, proved serologically.[6] Jaundice is rarely intense and usually disappears in about three weeks. Vomiting is rarely a serious problem; urine and feces are usually not strikingly abnormal. Liver enlargement is present in only about 15% of the cases and is rarely great. There is usually little liver tenderness.

The cephalin flocculation test is almost always positive in mononucleosis, but the serum bilirubin level is usually less than 1.0 mg. per 100 c.c. in nonjaundiced patients, and is rarely higher than 8.0 mg. in jaundiced patients. Other writers [1c] have reported similar observations. Since some of the liver function tests may yield normal results in mononucleosis,[1d] and since they do not parallel the degree of liver damage, we must look to histopathology to reveal the nature and the degree of involvement of the liver in infectious mononucleosis.

The essential data pertaining to liver involvement are shown in table 1.

One typical nonjaundiced patient and the three jaundiced patients will now be reported in greater detail.

Case Reports

Case 1. A 21 year old soldier became ill on August 24, 1954. Chief symptoms were chilliness, fever, sore throat, malaise and anorexia. Examination disclosed moderately enlarged, slightly tender lymph nodes in the anterior and posterior cervical and occipital regions bilaterally. Tonsils were moderately enlarged, inflamed and spotted with yellow patches. A palatal enanthema and sagging upper eyelids were present. Liver and splenic enlargement and tenderness were absent. Total leukocytes were 17,600, with 79% lymphocytes, of which nearly all were atypical. Heterophil antibody titer rose from 1:28 on September 1 to 1:56 on September 7, with a titer of 1:28 after guinea pig kidney absorption. Fever lasted nine days. Chest x-rays and three electrocardiograms were normal. Cardiolipin test was negative. Needle biopsy of the liver was performed eight days after onset of illness.

Comment: Clinically this case was typical of all the nonjaundiced patients. The changes in the differential leukocyte count were characteristic. The titer of heterophil antibodies was not typical, since all other patients had titers, after guinea pig kidney absorption, of 1:112 or higher. (This patient's case history, and others reported previously,[2] illustrate why we

believe the diagnosis of infectious mononucleosis is confirmed by a heterophil antibody titer of 1:28 after guinea pig kidney absorption.)

Case 8. A 24 year old soldier became ill on December 19, 1953, with malaise, headache, anorexia, slight sore throat and chilliness. On admission on December 22, 1953, he had a fever of 101.4° F. and slight enlargement of all cervical lymph nodes; his throat was slightly inflamed. There was questionable jaundice; a slightly tender liver edge was felt 2 cm. below the right costal margin. On December 23 jaundice was unquestionable; by January 11, 1954, jaundice had disappeared. (Serum bilirubin reached a peak of 8.0 mg.% on December 24, 1953, then quickly declined to 0.3 mg. on January 12, 1954.) Pharyngitis, tonsillar inflammation and generalized lymph node enlargement worsened until December 27, when he began to improve.

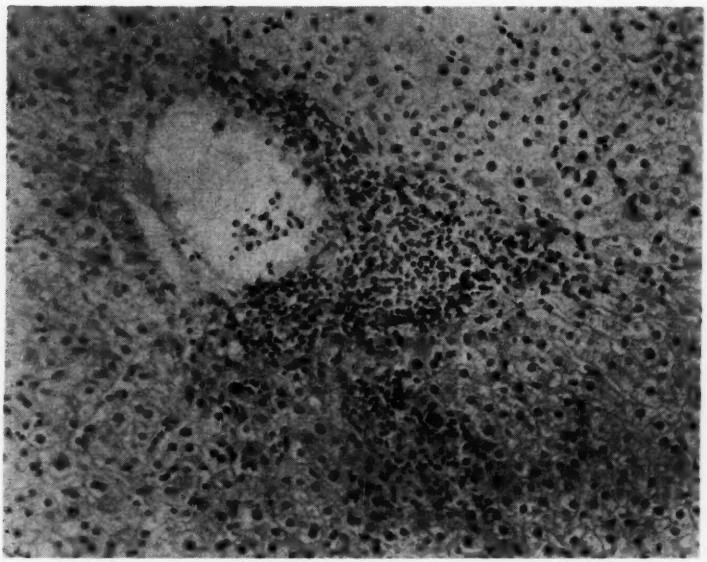

FIG. 1. Low power showing amount of portal infiltrate in average case. Note the normal appearance of the hepatic cells.

On December 29 and December 30 a generalized, slightly pruritic, pink maculopapular rash was present. On December 31 he was afebrile and felt well. On admission, leukocytes were 9,900 per cubic millimeter, with 54% lymphocytes (many atypical). On January 2, 1954, leukocytes were 13,700; 83% were lymphocytes, of which most were atypical. On January 2 heterophil antibody titer was 1:3,584 and 1:1,792 after guinea pig kidney absorption. Electrocardiograms, chest x-rays and cardiolipin test were all normal. Needle biopsy of the liver was performed 45 days after onset of illness, 19 days after he had left the hospital.

Comment: This patient's serum bilirubin level was the highest of any in our series, but it became normal within three weeks. The clinical, hematologic and serologic manifestations of infectious mononucleosis were

typical except for his rash which, in our experience, is rarely seen in infectious mononucleosis.[2] (We have thus far observed only three instances in an experience of about 300 cases.) In this case, it was decided to perform the needle biopsy after 19 days of ambulation, whereas in the cases to follow biopsies were performed earlier.

Case 9. A 20 year old soldier became ill on January 25, 1955, with severe sore throat, chilliness and fever. Six days later he noticed yellow eyes, dark urine and light feces. He was not admitted until the fifteenth day of his illness, when inflammation and a moderate generalized lymph node enlargement were noted. The liver was not tender, but its edge was felt 3 cm., and the splenic edge 4 cm. below the costal margins. Fever disappeared 20 days after onset of illness, and jaundice disappeared 15 days after first noticed.

On admission the blood count showed 12,400 leukocytes, of which 79% were lymphocytes (the majority atypical). Heterophil antibody titer was 1:896 and 1:448 after guinea pig kidney absorption. Chest x-ray, two electrocardiograms and cardiolipin test were all normal. Needle biopsy was performed on the twenty-first day after onset of illness.

Comment: Clinical, hematologic and serologic criteria for diagnosis for infectious mononucleosis were fulfilled. Intensity of jaundice was mild and duration was brief.

Case 10. A 24 year old soldier became ill on June 4, 1954, with fever, chilliness and malaise. Three days later he became nauseated, vomited after eating, and noticed dark urine and very light feces. On admission on June 9, 1954, he had a fever of 100.2° F. and was slightly jaundiced. Other signs were slight generalized lymph node enlargement, slight liver tenderness and questionable enlargement. There was no pharyngeal inflammation or splenic enlargement. During the next 10 days lymph node enlargement increased and the spleen became palpable. Jaundice disappeared 10 days after admission (15 days after onset of illness). Fever was present for 12 days; it did not exceed 99° F. during the last three days.

On the seventh day of illness a blood count revealed 13,200 leukocytes, of which 80% were lymphocytes; many lymphocytes were atypical. Heterophil antibody titer was 1:224, and 1:112 after guinea pig kidney absorption. Chest x-ray, three electrocardiograms and a cardiolipin test gave normal results. Needle biopsy of the liver was done on the eighteenth day after onset of illness.

Comment: Clinical, hematologic and serologic criteria for diagnosis were fulfilled. Intensity of jaundice was mild, duration was brief.

Discussion of Case Reports: Jaundice, when present, was mild and lasted only between two and three weeks. During the period of jaundice, patients were allowed bathroom privileges and other liberties consistent with degree of illness. As soon as fever disappeared, patients were allowed to become completely ambulant.

All three jaundiced patients became icteric in the latter half of the first week of illness. Inasmuch as only about one fifth of our patients with infectious hepatitis have elevated temperatures, the diagnosis of infectious mononucleosis should be considered whenever painless, mild jaundice is seen in a young *febrile* patient. If there is moderate lymph node enlargement, the suspicion of infectious mononucleosis is strengthened; and if, in

addition, acute pharyngitis or tonsillitis is present, the diagnosis of infectious mononucleosis is likely to be correct, even before a blood count is reported. If a blood count reveals that over 50% of the leukocytes are lymphocytes, and if atypical lymphocytes are present, little doubt exists that the heterophil test will be diagnostic of mononucleosis.

PATHOLOGY

All of the biopsies were performed with the Vim-Silverman needle. The specimens were allowed to adhere to a piece of filter paper to prevent curling and were then placed in 10% formalin. The tissue was embedded

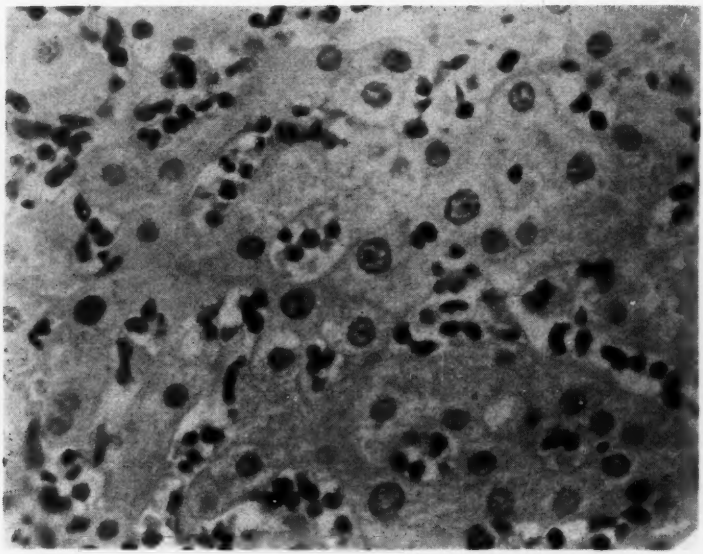

FIG. 2. High power showing the lymphocytes within sinuses and swelling of Kupffer's cells.

in paraffin and stained with hematoxylin and eosin. The average specimen measured about 2.0 cm. in length and slightly more than 1.0 mm. in diameter. There were no gross abnormalities.

There were 11 biopsies obtained from 10 patients. The day of clinically apparent illness on which the biopsy was performed is indicated in table 1.

The pathologic changes were very similar in all cases, so a description of each case, separately, is pointless. The most striking change was the presence of large numbers of mononuclear cells in the portal areas and throughout the lobules within sinuses. Many of the cells had the appearance of typical small lymphocytes, but there were also larger cells with

slightly vesicular nuclei and more abundant cytoplasm, which probably correspond to the atypical lymphocytes seen in the peripheral blood. In four cases small numbers of eosinophils were present in the portal exudate. Neutrophils were virtually absent, and plasma cells were not seen. The amount of portal infiltrate showed considerable variation.

In eight of the 10 cases small accumulations of mononuclear cells and lymphocytes were located at random within the lobule. The number of such foci was small in every case. These foci were associated with necrosis or displacement of only a few hepatic cells. Aside from this, evidence of hepatic cell damage was minimal.

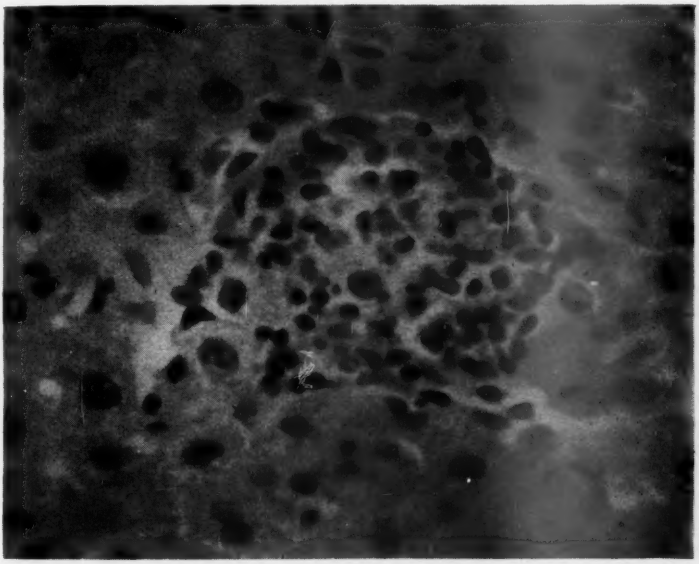

FIG. 3. High power showing intralobular collection of mononuclear cells and lymphocytes, with necrosis and displacement of some hepatic cells.

The hepatic cells showed very slight pleomorphism. There were a few slightly hyperchromatic enlarged nuclei. The amount of variation of hepatic cells probably did not exceed that seen in apparently normal livers, as recently described by Dunlap.[7] In five cases a small number of vacuolated nuclei were seen, indicating increased nuclear glycogen. Eosinophilic degeneration of hepatic cells was extremely rare. In only one case (case 7, table 1) did the picture differ significantly from the others. In this case there was moderate fatty change in addition to the other features described. Subsequent to the biopsy, a history of excessive alcoholic intake and inade-

quate diet for several months was elicited, which undoubtedly accounted for this fatty change.

In none of the cases was there distortion of architecture, bile stasis, bile duct proliferation or dilatation or fibrosis. The hepatic architecture was essentially intact except for mild encroachment on the peripheral part of the lobule by portal exudate. The Kupffer cells appeared slightly swollen in many cases. No endophlebitis was present. In one case biopsy was performed twice, on the fourteenth and the thirty-fourth days. The second biopsy showed moderate reduction in the amount of cellular infiltrate; no additional features were noted. The pathology in the patients with and without jaundice was essentially the same.

In summary, it may be said that all of the livers examined showed abnormalities in the form of lymphocytic infiltration, with only minimal hepatic cell changes and without alteration of hepatic architecture.

Discussion

There have been several descriptions of the histopathologic changes occurring in the liver in infectious mononucleosis, based on biopsy and autopsy material. These descriptions agree, in general, with those observed in the present series. Most authors have described the hepatic cell changes as being relatively slight. In an interesting article by Benazet,[8] the pathologic changes in the liver in nine cases of mononucleosis were compared with those seen in 14 cases of infectious hepatitis. The author pointed out that the infiltration of mononuclear cells, the swelling of Kupffer cells and small intralobular collections of mononuclear cells are common to both diseases. Changes in the parenchymatous cells, however, were conspicuous in infectious hepatitis, whereas they were minimal or absent in infectious mononucleosis. The author considered the difference so striking that he suggested that in problematic cases liver biopsy may be employed for differential diagnosis between these two diseases. Bertrand reported on the findings observed in liver biopsies in five cases of infectious mononucleosis without jaundice. He pointed out the resemblance to the liver changes seen in leukemia. He described small intralobular collections of lymphocytes and monocytes associated with displacement or necrosis of a few hepatic cells, and emphasized that this was the only form of hepatic cell necrosis seen in infectious mononucleosis. He expressed the nature of the change in the liver by use of the term "mesenchymal hepatitis."

In an excellent review [3] of the general pathology of infectious mononucleosis, based on autopsy material as well as biopsies, similar changes in the liver are described. An additional abnormality noted in autopsy cases was infiltration of the capsule by lymphocytes. This change cannot usually be observed in biopsies, as they do not include capsule.

Several other authors have described similar changes in the liver in cases of mononucleosis. Kass [9] reported one fatal case (with death due to rup-

ture of the spleen) in which he described loss of intralobular structure, some pleomorphism of hepatic cells and some nuclear variation, as well as increased numbers of mitotic figures, but no necrosis. Some of these changes may have been post mortem or the result of shock. Bang [10] reported on liver biopsies in four cases of mononucleosis without jaundice. He observed minor changes in the hepatic cells: slight variation in size and shape of nuclei, indistinct cellular borders and a few mitotic figures. His conclusion was that the changes have about the same appearance as those seen in acute epidemic hepatitis, but with less pronounced "parenchymatous and a little more severe interstitial changes." We believe the minimal degree of parenchymatous change should be emphasized more strongly. Sharp [42] reported on a fatal case, with death on approximately the thirty-eighth day of illness. Death was attributed to pneumothorax. In addition to infiltration in the liver, the hepatic cells were described as showing slight generalized cloudy swelling. Van Beek [11] reported on a liver biopsy in one case, taken on the fourteenth day of illness. He commented on the resemblance of the changes to those seen in leukemia. He also described increased numbers of mitotic figures in hepatic cells. No other mention of hepatic cell changes was made. A subsequent biopsy three weeks later revealed an essentially normal liver.

Kalk,[12] writing on the liver changes observed in biopsy material, commented that the peculiarity of hepatitis seen in mononucleosis was that only the mesenchymal structures were affected, while the hepatic cells either were not affected or were affected to only a very slight extent. He stated further that there is no tendency to connective tissue proliferation, and consequently no tendency to development of postnecrotic cirrhosis. As far as we know, only one case of cirrhosis of the liver following infectious mononucleosis has been reported in the literature.[13] The causal relationship in this case is, in our opinion, open to question. In this regard, it is interesting to speculate on the possible future development of cirrhosis in our case 7 (table 1). Without knowledge of the biopsy changes such a cirrhosis might be attributed to infectious mononucleosis, rather than to fatty change.

In contrast to most of the observations on liver changes in infectious mononucleosis are those described by Wadsworth et al.[14] These authors described considerable hepatic cell damage in cases of infectious mononucleosis, similar to that seen in nonfatal cases of infectious hepatitis. They described scattered hepatic cells or groups of hepatic cells showing eosinophilic degeneration. This change has been described by Mallory [15] as characteristic of nonfatal cases of infectious hepatitis. The authors considered the time of biopsy to be important, stressing that the maximal changes were observed between the tenth and thirtieth days of illness. However, in the present series eight biopsies were obtained during that period and virtually no such changes were observed. Furthermore, many of the cases reported by other authors included biopsies taken during that period.

In summary, our observations agree with those of the majority of investigators, who have described changes in the liver consisting of lymphocytic infiltration with relatively slight changes in hepatic cells, and essentially no change in hepatic architecture. In contrast to the average case of infectious mononucleosis, the average biopsy specimen of infectious hepatitis is characterized by significant necrosis of hepatic cells as well as inflammatory infiltrate. The pathologic changes in mild cases of infectious hepatitis can, however, be essentially the same as in infectious mononucleosis.

Conclusions

1. Clinical experience, including follow-up periods of two to three years, has indicated that nonjaundiced patients with mononucleosis can be ambulated rapidly, and that jaundiced patients need not be managed so rigidly as patients with infectious hepatitis.

2. This investigation showed that the hepatitis of mononucleosis, which is somewhat different from that of infectious hepatitis, is characterized by lymphocytic infiltration, minimal hepatic cell damage and no architectural change. Accordingly, there is histopathologic support for the liberal management of mononucleosis patients, with and without jaundice.

3. Painless jaundice in young adults may be due to infectious mononucleosis when mild and associated with fever. If it is also associated with pharyngitis and lymph node enlargement, it is likely that hematologic and serologic confirmation of mononucleosis will be obtained.

Summario in Interlingua

Le involvimento del hepate in mononucleosis es un characteristica del morbo que occurre regularmente e non pote esser considerate como un complication. Esseva executate investigationes bioptic a agulia con le objectivo de determinar si studios histologic supportarea le conception, basate super experientias clinic, que le hepatitis de mononucleosis es usualmente leve. Secundarimente le autores voleva facer un contribution al litteratura del hepatobiopsias in mononucleosis, nam iste litteratura es magre.

Omne le patientes satisfaceva le requirimentos clinic, hematologic, e serologic del diagnose. Tres patientes esseva includite proque illes habeva ictero; le remanente septe patientes esseva investigate consecutivemente. Le ictero, quando presente, esseva leve e durava solmente duo o tres septimanas. Si tosto que le febre dispareva, omne le patientes habeva le permission de ambular liberemente, excepte que durante le ictero le patientes habeva solmente le privilegio de render se al W.C.

Le autores ha constatate que solmente circa un quinto de lor patientes con hepatitis viral ha febre. Isto suggere que le diagnose de un altere hepatitis viral—i.e., del hepatitis debite a mononucleosis—deberea esser considerate ubicunque non-dolorose e leve formas de ictero occurre in un juvene adulto con febre, specialmente si le allargamento del nodos lymphatic es plus que minimal. Si acute pharyngitis o tonsillitis es etiam presente, ill es probabile que le suspicion de mononucleosis va confirmar se per alterationes del cellulas sanguinee e per le reaction a anticorpores heterophile.

Le biopsias esseva executate per medio del agulia de Vim-Silverman. Omne le biopsias, con un sol exception, esseva executate inter le 8te e le 19ne die del morbo.

Le alterationes observate esseva simile in omne casos. Le plus frappante observation esseva le presentia de grande numeros de cellulas mononuclear in le areas portal e ubicunque in le lobulos intrasinusal. In quatro casos parve numeros de eosinophilos esseva presente in le exsudato portal. Le quantitate del infiltrato portal variava. In octo casos alicun parve accumulationes de cellulas mononuclear esseva trovate al hazardo intra le lobulo. Iste focos non esseva associate con necrosis o displaciamento de plus que alicun pauco numerose cellulas hepatic. Alteremente le signos de lesiones del cellulas hepatic esseva minimal. Un specimen monstrava moderate alterationes adipose ultra le characteristicas de occurrentia regular. In iste caso il esseva constatate post le biopsia que le patiente habeva un historia de excessos alcoholic e de dieta inadequate. Assi le alterationes adipose poteva explicar se. Si iste patiente disveloppa cirrhosis al futuro, le causa non debe esser cercate in le mononucleosis sed in su alcoholismo—providite que illo perdura.

Nulle specimen revelava distortiones architectural, fibrosis, endophlebitis, stasis biliari, o proliferation o dilatation del vias biliari. Un del patientes esseva subjicite al biopsia duo vices—le 14te e le 24te die del morbo. Le secunde biopsia monstrava un moderate reduction quantitative del infiltrato cellular e nulle symptomas additional. Le lesiones in patientes con e sin ictero esseva in principio le mesmes.

Le autores conclude que—ben que hepatitis occurre regularmente in mononucleosis—il non es necessari que le patientes (mesmo illes con ictero) es subjicite a un regime tanto rigide como le patientes con hepatitis infectiose, proque le curso clinic es plus leve e le histopathologia—in tanto que demonstrate per nostre biopsias—involve nulle significative lesiones parenchymal.

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JAUNDICE IN CARDIAC FAILURE WITHOUT INFARCTION *

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THIS is a description of a series of cases in which jaundice was present as the result of heart failure. The occurrence of jaundice in cardiac insufficiency is usually considered secondary to a recent infarct of the lung, spleen or kidney. Jaundice occurring in heart failure without infarction of these organs has been insufficiently emphasized. Recognition of this entity has become particularly important since the widespread use of anticoagulants in the therapy of embolic complications of heart disease. In the presence of jaundice due primarily to severe liver disease in cardiac failure, the use of anticoagulant drugs is not indicated.

White,[1] Rolleston and McNee,[2] Bockus [3] and Halsted and Bauer [4] mentioned jaundice in heart failure due solely to the disordered function of the liver without pulmonary infarction. Ernstene [5] pointed out that acute necrosis of the liver with jaundice can occur in severe chronic congestive heart failure.

Kugel and Lichtman [6] stressed the rarity of jaundice without pulmonary infarction in heart failure. In 273 postmortem examinations of patients with congestive heart failure they found only one case with clinical jaundice. They did not mention serum bilirubin values. Gomes et al.[7] reported on two patients in severe congestive failure with extensive liver damage, jaundice and no autopsy evidence of infarction. Other authors [8, 9, 10] have discussed the occurrence of jaundice in chronic congestive heart failure without mentioning pulmonary infarction.

Though the group of patients presented is too small for a significant statistical study, it is interesting to note that all except one had severe rheumatic heart disease. These 10 patients with rheumatic heart disease had as a common finding severe involvement of the mitral valve. Other valvular lesions were present in varying combinations. A long standing, right-sided heart failure resulting from this type of valvular disease was characteristic of these patients. Eight of the total of 11 patients also had auricular fibrillation, and all except two had had severe congestive failure longer than two and one-half years. The other two were of one month's and five months' duration. This extremely severe and chronic congestive failure is the usual finding in the condition under discussion here. One patient had an embolus of the right branch of the pulmonary artery to the right lower lobe without any evidence of infarction.

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Two of the patients had evidence of chronic cholecystitis without obstruction or cholangitis. All 11 patients had evidence of severe liver damage. Eight had cardiac cirrhosis varying from the early to the far advanced stages. The remaining three had extreme congestion, necrosis and marked destruction of the normal hepatic structure without evidence of cardiac cirrhosis.

Of these 11 patients, two had received Dicumarol, one for eight weeks and the other for three weeks, shortly before death. The first of these (Case 1) had fever, pleuritic pain, blood-tinged sputum and signs of severe

TABLE 1

Age	Sex	Duration of Failure	Clinical Findings	Bilirubin Values in Milligrams %	PM Diagnosis	Liver Weight
1. 38	F	6 years	Auricular fibrillation and severe cardiac failure	1.6 mg. indirect	Rheumatic heart disease with mitral, aortic and tricuspid stenosis. Cardiac cirrhosis.	1,250 gm.
2. 60	F	3 years	Auricular fibrillation, severe cardiac failure and cyanosis	2.3 mg. indirect	Rheumatic heart disease with mitral, aortic and tricuspid stenosis. Cardiac cirrhosis.	2,150 gm.
3. 37	M	6 years	Auricular fibrillation, severe cardiac failure	1.6 mg. direct	Rheumatic heart disease with mitral, aortic and tricuspid stenosis and insufficiency. Early cardiac cirrhosis.	1,560 gm.
4. 20	M	3 years	Regular rhythm, severe cardiac failure and icterus	6.0-10.5 direct	Rheumatic heart disease with mitral and aortic stenosis and insufficiency. Extreme congestion of central areas of liver with necrosis of liver cells.	1,300 gm.
5. 24	F	6 years	Auricular fibrillation and severe cardiac failure	5.3 direct	Rheumatic valvulitis with mitral, aortic and tricuspid stenosis and insufficiency. Cardiac cirrhosis.	1,130 gm.
6. 61	M	4 weeks	Regular rhythm, moderate cardiac failure, icterus and cyanosis	4.9 direct	Syphilitic aortitis with aneurysm of arch of aorta. Fistula between aortic and superior vena cava. Congestion of central veins.	1,150 gm.
7. 54	F	2½ years	Auricular fibrillation and severe cardiac failure	7.0 direct	Rheumatic heart disease with mitral, aortic and tricuspid stenosis and insufficiency. Cardiac cirrhosis.	1,800 gm.
8. 10½	M	5 months	Regular rhythm, severe cardiac failure and icterus	Not done	Rheumatic heart disease with mitral stenosis and insufficiency. All central areas of liver showed extensive necrosis.	1,310 gm.
9. 42	F	6 years	Auricular fibrillation, severe cardiac failure and icterus	1.9 direct	Rheumatic heart disease with mitral stenosis and insufficiency. Cardiac cirrhosis.	2,500 gm.
10. 72	M	6 years	Auricular fibrillation, severe cardiac failure and cyanosis	1.5 indirect	Rheumatic heart disease with mitral and aortic stenosis. Cardiac cirrhosis.	1,750 gm.
11. 33	F	13 years	Auricular fibrillation and severe cardiac failure	1.8 direct	Rheumatic heart disease with mitral, aortic and tricuspid stenosis and insufficiency. Cardiac cirrhosis.	1,600 gm.

failure. On the basis of these signs and other nonconclusive evidence she was considered to have a pulmonary infarct and was so treated. At autopsy no infarct was present. The second patient (Case 11) was placed on Dicumarol because the fever, pleural friction rub, blood-tinged sputum and crepitant râles at the right base were considered due to a pulmonary infarct. These findings were explained by the postmortem demonstration of pneumonitis and pressure atelectasis of the right as well as the left lower lobe.

Jaundice occurred in the last few months of life in the majority of our patients. The appearance of a severe degree of bilirubinemia is an ominous

sign, and was usually followed by the death of the patient in a few weeks. Those patients with a milder degree of jaundice lived for many weeks before succumbing to their cardiac disease. Their jaundice persisted until the end. Pruritus was a very minor complaint. It must be remembered that these extremely ill patients might not react to bilirubin retention as would relatively normal people.

Other liver function tests performed in these patients are recorded in table 2. Two had serum bilirubin determination as their only liver function test. One patient died so soon after admission that even this was not done, but intense jaundice was present. This group of patients and tests is so small that, obviously, no conclusions can be drawn. An earlier study [11] on 135 patients in chronic congestive heart failure, with 54 autopsies, revealed an abnormality of the Bromsulphalein test in 85%, of the bilirubin in 52%, and of alkaline phosphatase in 46%. The other liver function tests were abnormal in only one third or less of the patients. Of the autopsied

TABLE 2

Patient Number Patient's Age	1 38	2 60	3 31	4 20	5 24	6 61	7 54	8 10½	9 42	10 72	11 33
Total protein, gm. %	6.2	6.3	6.5	6.8	6.8	6.4	6.1			7.8	
Albumin, gm. %	3.9	3.7	3.6	4.2	3.8	3.8	3.3			4.7	
Globulin, gm. %	2.3	2.6	2.9	2.6	3.0	2.6	2.8			3.1	
Cholesterol, mg. %	117		190		144	167				216	
Cholesterol esters, % esterification	59		58		30	60				69	
Cephalin flocculation, 0–4+	2+	Neg.	1+ to 3+	3+ to 4+	Neg.	Neg.				4+	
Thymol turbidity, units	5	4	4.8	4	4	4				10	
Alkaline phosphatase, Bodansky units	4.0	10.6	7.7 to 14.4	3.5	5.9	3.0				10.1	
Bromsulphalein, % retention in 30 minutes	50				50						

patients with cardiac cirrhosis, the alkaline phosphatase was abnormal in 85% of the determinations.

Why cardiac failure produces hepatic damage and subsequent jaundice can be explained only by a combination of factors. There is a mechanical factor as a result of elevated venous pressure and resultant increased pressure in the liver. An analogous condition in the liver was experimentally obtained by Zimmerman and Hillsman.[12] They produced hepatic necrosis in dogs by constricting the inferior vena cava with metal bands. The degree of hepatic necrosis varied directly with degree of obstruction. This was likened to the factor of obstruction produced by passive congestion in the liver.

Resnik and Keefer [13] believe that anoxemia is also an extremely important factor in producing central necrosis and jaundice. This view is supported by a consideration of the anatomic findings. As pointed out by Ottenberg,[14] the pressure is higher at the periphery of the lobules, where

the blood from the portal veins and hepatic artery enters. If pressure were the only important cause, one would expect to find atrophy in the periphery rather than at the center of the liver lobule. The main oxygen supply of the liver cells is from the hepatic artery. Stead and his group [15] found that in chronic heart failure there is a 33% decrease in splanchnic blood flow. Due to an increased A-V oxygen difference, consumption appears to be about normal. As the blood enters at the periphery, it may well be that by the time the blood reaches the cells at the center of the lobules the oxygen tension here is insufficient to sustain the life of all of the cells.

The elevated venous pressure and anoxemia in the liver in severe congestive failure can explain the resultant hepatocellular damage with necrosis and cardiac cirrhosis. In addition, in severe chronic congestive heart failure there is increased red cell destruction secondary to stasis, with increased pigment deposition.[17] This increased bilirubin formation, and the extensive anatomic liver changes, are the important factors in the production of jaundice.

The differentiation of jaundice without infarction is frequently difficult. As recorded, two of the patients presented were incorrectly considered to have pulmonary infarction and were treated with anticoagulants. We believe that the presence of jaundice in severe congestive failure, usually of a chronic nature, coupled with signs of liver disease, should arouse a strong suspicion of the entity under discussion. In addition, when there are no good roentgenologic or other clinical signs of pulmonary infarction, or definite evidence of renal or splenic infarction, the jaundice usually can be explained on the basis of hepatic disease. Although the diagnosis has been made infrequently heretofore, we believe that it can be made. Since the anticoagulants are of no benefit in this condition, there is no valid reason for their use.

Jaundice in cardiac patients does occur without infarction. It can occur secondarily to cardiac cirrhosis or necrosis of the hepatic cells. Since jaundice can be overlooked in a cyanotic patient,[16] it is important to determine the serum bilirubin values in any suspect case. Another difficulty, as Meakins [17] pointed out, is that jaundice does not appear in the skin over areas where edema was present. Once jaundice is recognized in a cardiac patient, it is extremely important to have good proof of an embolus before instituting anticoagulant therapy.

Conclusion

1. Autopsied patients dying of severe cardiac failure with jaundice in the absence of pulmonary, splenic, renal or other infarcts are presented.

2. The jaundice was secondary to cardiac cirrhosis or severe liver necrosis.

3. The majority of the patients presented had rheumatic heart disease and auricular fibrillation.

4. Anticoagulant therapy should not be instituted in cardiac patients with jaundice unless excellent evidence of pulmonary, renal or splenic infarction is present.

Summario in Interlingua

Es presentate un serie de 11 autopsiate patientes in qui ictero esseva presente como resultato de lesion hepatic secundari a disfallimento cardiac. Isto occurreva in le absentia de infarcto de pulmone, splen, o ren. Omne patientes, con un exception, habeva sever rheumatic morbo cardiac. Iste 10 patientes monstrava marcate involvimento del valvula mitral e avantiatissime disfallimento congestive. Le 11me patiente habeva moderate congestive disfallimento secundari a un aneurysma syphilitic del arco del aorta, con un fistula inter le aorta e le vena cave superior. Octo del 11 patientes habeva fibrillation auricular. In 9 casos disfallimento congestive habeva essite presente durante plus que duo e medie annos. Omne 11 patientes exhibiva sever damnos hepatic. Octo habeva cirrhosis cardiac, ab le prime al plus avantiate phases. Le altere tres habeva necrosis e marcate destruction del normal structura hepatic sin signos de cirrhosis cardiac. Ictero occurreva durante le ultime menses del vita e non recedeva ante le morte. Prurito esseva de signification minor in iste maladissime patientes. Le bilirubina seral variava ab 1,5 mg pro cento in reaction indirecte a 10,5 mg pro cento in reaction directe.

Ictero in disfallimento cardiac es causate le plus probabilemente per un combination del sequente tres factores: (1) Factor mechanic resultante del elevation del pression venose con augmentate pressiones in le hepate. (2) Reducite tension de oxygeno in le sanguine que attinge le cellulas al centro del lobulos hepatic. (3) Augmentate destruction de erythrocytos secundari a stasis con augmentate deposito de pigmento. Ictero in casos de sever disfallimento congestive sin clar signos clinic o roentgenologic de infarcimento pulmonar, renal, o splenic es usualmente explicable super le base de damno hepatic. In iste condition clinic, anticoagulantes non deberea esser usate.

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"CHOLANGIOLITIC HEPATITIS," WITH SPECIAL REFERENCE TO ITS PHYSIOPATHOLOGIC CONCEPT, DIAGNOSIS AND THERAPY *

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THE increasing incidence of and interest in hepatitis in the last decade is clearly discernible from the constantly rising volume of literature on the subject. In the past several years we have encountered numerous cases of jaundice in various age groups in which the correct diagnosis became apparent after a brief survey, including various laboratory procedures in conjunction with a short period of clinical observation. In several cases, however, the history and the laboratory studies left the clinical picture sufficiently confused as to necessitate more involved diagnostic procedures, such as cholangiography, liver biopsy and even exploratory laparotomy.

These patients presented the usual clinical picture of jaundice, with an appreciable degree of pruritus and some degree of hepatomegaly. Hyperbilirubinemia and bilirubinuria, with only a slight to moderate increase in the blood alkaline phosphatase, were the sole abnormal laboratory findings. Unlike the results in the usual types of cases of infectious hepatitis, liver function tests in these cases gave no evidence of hepatocellular damage. On the basis of our observations it became apparent to us that we were dealing with a type of jaundice aptly described by Watson and Hoffbauer [1] as "cholangiolitic hepatitis." A realization of the difficult diagnostic problem this type of hepatitis may present and the important therapeutic implications involved prompted us to report the following two representative cases. A brief discussion of a concept of the physiopathologic alterations and of the rationale of therapy based on this concept will be furnished under "Comments."

CASE REPORTS

Case 1. A 41 year old white female entered the Beth El Hospital on December 14, 1954, with the chief complaints of jaundice, marked fatigue, pruritus and tenderness in the right upper abdominal quadrant and epigastrium. She had been well until six weeks prior to admission, when she developed vague epigastric pains radiating to the precordium and left scapula, not related to meals or effort. This lasted about four days, subsiding completely only to reappear three weeks later in a more severe form, manifested by epigastric pressure after meals requiring Alka Seltzer for relief, and associated with generalized bodily aches, lassitude, chilly sensations and fever. Her physician treated her for an "intestinal virus" infection, for which she was given a penicillin injection, with subsidence of the fever on the third day. Twelve days before entering the hospital she developed nausea and vomiting and jaundice. The urine became dark brown, while the stools remained

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normal in color. Simultaneously with the above she developed an intense generalized pruritus, marked fatigue, anorexia and a weight loss of 12 pounds. The family history was unimportant. Her past history, with the exception of a perineorrhaphy six years ago, was irrelevant. She had been taking no medication and receiving no injections prior to the onset of the present illness.

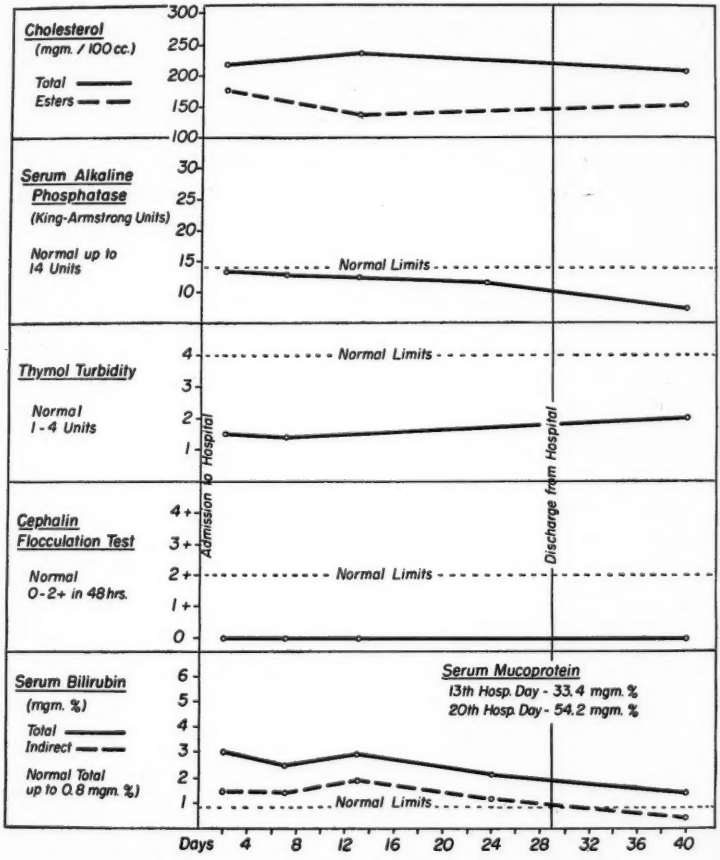

FIG. 1. Liver function tests of Case 1 at Hospital and 2 weeks after discharge.

Physical Examination: This revealed an intensely jaundiced, anxious and acutely ill female, well developed but showing evidence of weight loss. Diffuse excoriations resulting from the pruritus were noted over the body and extremities. No lymphadenopathy was evident. The lungs were normal to percussion and auscultation. The heart was of normal size and rhythm, revealing a grade II, soft systolic apical murmur. The blood pressure was 168/82 mm. of Hg. The abdomen was soft, and the liver edge was palpable about two fingerbreadths below the right costal margin,

in the midclavicular line, and was somewhat tender to palpation. The spleen was not palpable, and no other organs or masses were felt. No spider angiomas or peripheral edema was noted. The temperature on admission was 99.4° F.

Laboratory Examination: Urinalysis revealed 2 plus albuminuria, 4 plus bilirubinuria and the presence of urobilinogen in a dilution of 1:20. The stools were of normal color and showed the presence of urobilin. The hemoglobin was 12 gm. %, with a hematocrit of 38%. White blood cells, 9,800 per cubic millimeter, with the differential count showing a shift to the left. Erythrocyte sedimentation rate was 40 mm. per hour (Wintrobe), and prothrombin time was 82%. The blood chemistry values and liver function tests (figure 1) were as follows: fasting blood sugar, 110 mg. %; urea nitrogen, 10 mg. %; total proteins, 6.5 gm.; albumin, 3.5 gm.; globulin, 3 gm. %. Total cholesterol, 219 mg.; cholesterol esters, 179 mg. %. Total serum bilirubin, 3.0 mg., with direct reacting bilirubin, 1.5 mg. %. Alkaline phosphatase, 13.2 King-Armstrong units; thymol turbidity, 1.5 units; cephalin cholesterol flocculation test, negative in 48 hours. Serum mucoproteins,[2]* 33.4 mg. %. Electrocardiogram and chest x-ray were normal. Scout films of the abdomen revealed no calcific shadows in the right upper abdomen consistent with calculi. A Cholografin† study after intravenous administration of 40 c.c. of the contrast medium failed to reveal any dye within the liver radicles or in the extrahepatic ducts over a two hour period, the contrast medium appearing in the right kidney. Needle biopsy of the liver (figure 3) revealed a normal hepatic architecture and the presence of bile thrombi suggesting cholestasis. In spite of the normal liver function tests in the presence of jaundice, and because of the diminished serum mucoproteins, the lack of any evidence of extrahepatic obstruction and the findings of the liver biopsy, we felt we were dealing with a cholangiolitic hepatitis.

Clinical Course: The patient was kept on a high carbohydrate, moderate protein and low fat diet with parenteral vitamin supplements. Her general condition gradually improved, the anorexia and fatigue subsiding and the liver diminishing to almost normal size by the end of the fourth hospital week. At this time the jaundice was very definitely diminished and the bilirubin approached almost a normal level, with only traces of bile in the urine. A second serum mucoprotein determination revealed 54.2 mg. %, paralleling the general clinical improvement. She was discharged on January 10, 1955 (four weeks after admission), as markedly improved, and was advised as to convalescent care. Reëxamination two weeks later revealed no evidence of jaundice, normal urobilinogen, no bile in the urine and only a slight increase in the serum bilirubin (figure 1). A Cholografin study repeated three weeks after hospital discharge revealed good visualization of the extrahepatic ducts and gall-bladder and no evidence of any shadows suggestive of calculi.

Case 2. A 31 year old white female entered the Beth El Hospital on November 17, 1954, because of jaundice, epigastric distress, nausea, general debility and pruritus. About three years before she had been hospitalized for a jaundice caused by a common duct stone obstruction, at which time a cholecystectomy was performed, with uneventful recovery. Three weeks prior to the present admission she developed nausea and epigastric distress. One week before hospitalization she began to experience increased upper abdominal distress, persistent nausea, jaundice associated with a dark urine, and occasional chills with elevation of temperature up to 104° F. The stools were of normal color and the pruritus was mild in character. She was given antibiotics by her physician, with a subsidence of fever, although the jaundice became more intense.

*We are indebted to Dr. Ezra M. Greenspan of Mount Sinai Hospital, New York City, for the mucoprotein determinations.

†Cholografin, manufactured by E. R. Squibb and Sons, is a compound salt containing about 64% of iodine; prepared as a 20% isotonic solution, it is a suitable medium for intravenous cholangiography.

Physical Examination: This revealed a well developed and well nourished, acutely ill female, markedly icteric. There was no evidence of lymphadenopathy, spider angiomas or peripheral edema. The chest was normal to percussion and auscultation. The heart was of normal size, the heart sounds were of good quality and normal rhythm, and no murmurs were heard. The abdomen was soft, revealing

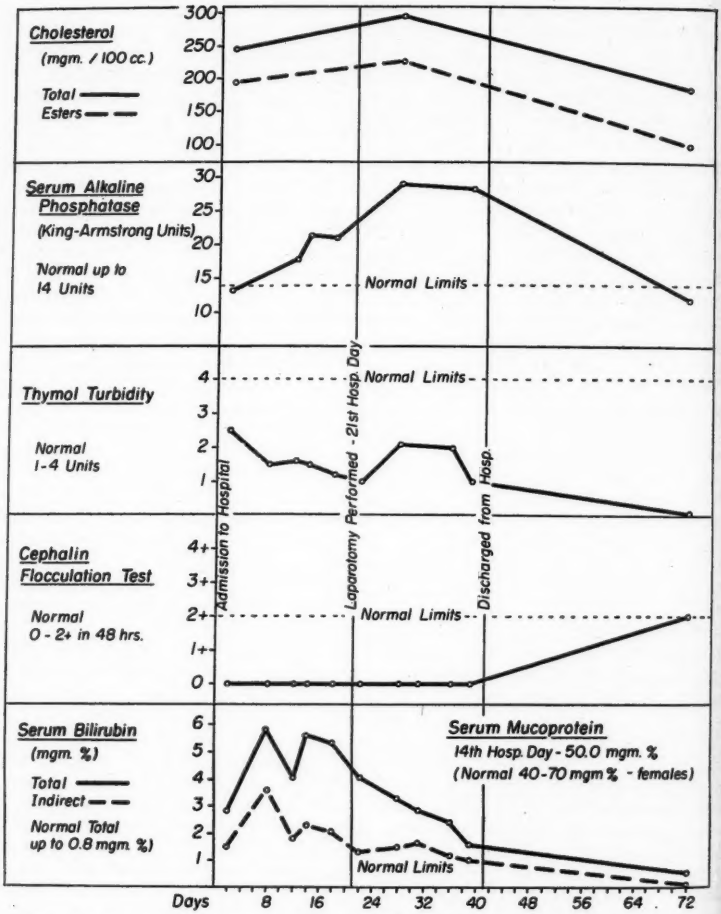

FIG. 2. Liver function tests of Case 2 at Hospital and 4 weeks after discharge.

no evidence of ascites or any palpable organs or masses. Some tenderness over the liver area was elicited on palpation. Temperature on admission was 99.6° F.

Laboratory Examination: Urinalysis revealed 4 plus bile and urobilinogen in 1:20 dilution. Stools were positive for urobilin. The hemoglobin was 12.8 gm.

%, with a hematocrit of 48%. White blood cells, 11,000 per cubic millimeter, with a normal differential count. The sedimentation rate was 42 mm. per hour (Wintrobe); the prothrombin time, 14 seconds (100%). The blood chemistry revealed a fasting blood sugar of 100 mg. %; urea nitrogen, 10 mg. %; total proteins, 6.6 gm.; albumin, 4.0 gm.; globulin, 2.6 gm. %. Total cholesterol, 243 mg. % (subsequently rising to 292 mg.); cholesterol esters, 192 mg. %. Blood lipase, 1.7 c.c.; blood amylase, 151 Somogyi units. Liver function tests (table 2) revealed serum bilirubin to be 2.85 mg., with direct reacting bilirubin, 1.5 mg. % (subsequently rising to 5.8 mg.). Alkaline phosphatase, 13.4 King-Armstrong units (rising to 29.0 units) (figure 2). Cephalin-cholesterol flocculation and thymol turbidity tests were repeatedly normal, and a zinc sulfate turbidity test was normal. Serum mucoproteins were 50.0 mg. % (low normal). X-ray of the chest and scout films of the abdomen were negative.

In view of the past history of cholelithiasis and the present laboratory findings of normal liver function tests and continuously rising serum bilirubin and alkaline phosphatase, we felt that a laparotomy was urgent to rule out extrahepatic obstruction.

Clinical Course: A laparotomy was performed on December 8, 1954, three weeks after admission. The common duct was exposed, and no stones or any other evidence of obstruction was found. Cholangiography was performed, revealing no evidence of calculi. A liver biopsy obtained at the operation (figure 4) was reported as "acute cholangiolitis with cholestasis," with presence of bile thrombi. A lymph gland removed from the omentum revealed lipoid granulomatous changes. The postoperative course was uneventful. A second cholangiography performed 12 days postoperatively again revealed no evidence of calculi in the common duct or in the liver radicles. The patient was discharged three weeks after operation, at which time the serum bilirubin had come down to 1.6 mg. %, although the alkaline phosphatase was still 28.2 King-Armstrong units. A follow-up examination four weeks later revealed no evidence of jaundice and normal laboratory findings (figure 2).

Comment

These two patients exemplify the difficulties which may be encountered in arriving at a diagnosis in some cases of jaundice. The importance of a correct diagnosis and its therapeutic implications hardly require emphasis. Surgery obviously is not only contraindicated but also may prove hazardous. Our clinical impression of the patient in case 1 was that of an infectious hepatitis. The results of the conventional liver function tests (table 1), with the exception of a bilirubinemia and an abnormal serum mucoprotein, failed to indicate hepatocellular damage unequivocally. Repeated tests revealed bile in the urine and normal concentrations of urobilinogen and the consistent presence of fecal urobilin. These findings obviously indicated obstruction, but ruled out complete biliary obstruction. A Cholografin study failed to outline the extrahepatic ducts, the medium being shunted back to the circulation and appearing in the kidney. Four weeks later this procedure revealed good ductal visualization. This failure of the biliary ducts to visualize in the presence of apparently normal functioning hepatic cells is an interesting phenomenon and will be briefly mentioned below. The liver biopsy (figure 3) revealed a normal hepatic architecture, con-

firming the absence of widespread cellular damage and the presence of bile thrombi, indicating cholangiolitic cholestasis.

In case 2 it may likewise be noted (figure 2) that the various liver function tests were normal, with the exception of an increased serum bilirubin, alkaline phosphatase and total cholesterol, indicating biliary obstruction. The low normal serum mucoprotein value rather favored the diagnosis of hepatitis. The urine revealed the presence of bile and urobilinogen in

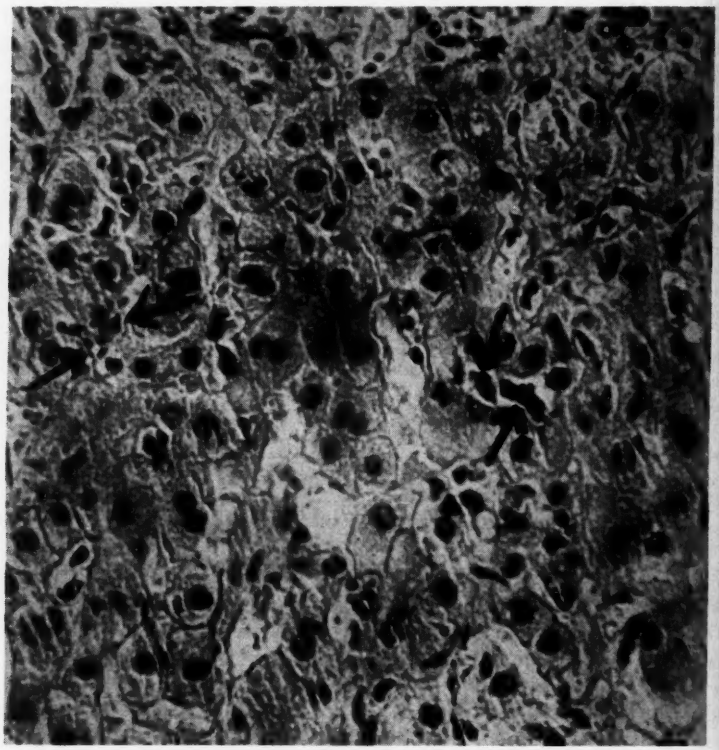

FIG. 3. Liver biopsy in Case 1, showing bile thrombi (arrows). Hepatic architecture appears intact.

normal dilutions, the latter furnishing evidence that there was neither complete obstruction nor extensive hepatocellular damage. With such dissociation of laboratory results and the past history of cholelithiasis, a common duct stone obstruction seemed a distinct possibility, one that was disproved only by exploring the ducts both surgically and angiochologra-phically. That we were dealing with an acute cholangiolitis with a cholestasis was verified by liver biopsy.

A comparison of the various findings in our two cases with the findings in the cases reported by Watson et al.[1] leaves little doubt as to the correctness of our diagnosis of "cholangiolitic hepatitis." Steigman and Popper [2] described a similar form of hepatitis which they termed "intrahepatic obstructive jaundice," ascribing the intrahepatic obstruction with jaundice either to a plugging of the cholangioli by bile thrombi, to actual increase in size of the liver cords, or to periportal cellular accumulations. These

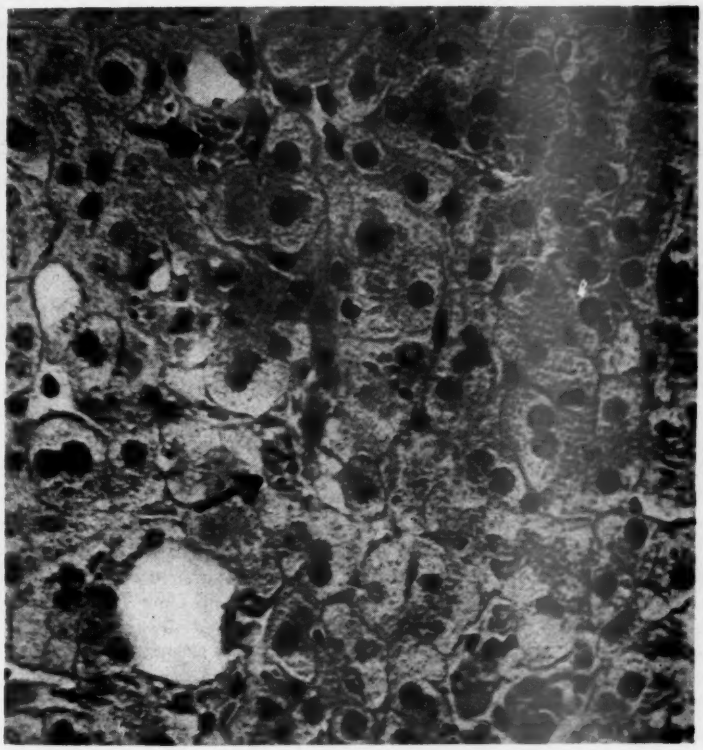

FIG. 4. Liver biopsy in Case 2, revealing bile thrombi (arrows). Hepatic architecture appears normal.

factors, in varying degrees, have been believed to obstruct in a mechanical way bile flow within the cholangioli. Watson,[1] however, points out that in some cases, at least, neither one of the above factors is too impressive a finding, or of sufficient magnitude to be the sole cause of the obstruction and the associated bile regurgitation. Instead, he offers a very attractive and what appears on existing evidence to be a logical cause for the regurgitation, namely, an increased permeability of the walls of the cholangioli.

The latter, having been injured by the causative agent, present a pathologic alteration analogous to the injured renal tubule which occurs in nephrosis. It may indeed be correct for us to propose the term "cholangiolosis" to indicate more specifically the anatomicopathologic alteration. That the increased permeability of the cholangioli, with escape of bile back into the circulation, is probably the prime factor in the disturbed liver physiology, and obstruction of cholangioli by bile thrombi of only secondary importance, is supported by the fact that even in severe cases of regurgitation jaundice (figure 4), bile thrombi are not sufficiently numerous to produce extensive intrahepatic obstruction. The occurrence of bile thrombi, to quote Watson,[1] "would fit well, however, with the concept of regurgitation of bile by leakage through damaged bile capillaries or ampullae, since it is logical to assume that in the course of such a "diapedesis" of bile, relatively more water and less solid would leak through into the spaces of Disse, with the result that whatever bile remained in the capillary would tend to become inspissated, thus favoring the formation of bile thrombi."

The concept of "cholangiolosis" may be of more than academic interest: it may be an important factor in effective therapy. The failure to visualize the bile radicles and extrahepatic ducts with Cholografin in case 1 lends support to the above concept. It is pertinent to point out here that this contrast medium, being delivered to the liver lobules and sinusoids via the capillaries of the hepatic artery at a pressure head of considerably above 300 mm. of water, encounters a lower pressure within these sinusoids, averaging about 165 mm. of bile.[4] Mitchell and Stifel [5] in producing total biliary obstruction by ligating the common bile duct in dogs, have shown that it required a pressure of 370 mm. of bile to cause complete cessation of bile secretion. Obviously these conditions did not exist in our patients, since such total suppression of bile secretion is found almost exclusively in malignant obstructions of the common bile duct. The assumption that failure of the contrast medium to reach the bile canaliculi may have been due to hepatocellular damage is untenable in the presence of normal liver function tests and the biopsy findings in our cases. It is then logical to assume that the contrast medium, having reached the canaliculi, because of their increased permeability leaked back into the circulation, appearing in the kidneys.

At this juncture it would not be amiss to make brief reference to the value of the serum mucoprotein determination as an aid in the differentiation of hepatogenic from obstructive jaundice. Mucoprotein is a carbohydrate-rich protein fraction, comprising about 1% of the total serum proteins in the normal state. It seems to be increased in the presence of proliferative or destructive processes anywhere in the body, but usually in extrahepatic sites. In liver involvement due to hepatitis or portal cirrhosis, the mucoproteins fall to below normal levels. The reason for the above is not clear. It is possible as pointed out by Greenspan et al.,[6] that in parenchymatous liver disease there may be either increased utilization or decreased formation

of mucoproteins. Reporting the results of mucoprotein determinations on a series of more than 2,000 patients, the above investigators found the normal values in females to range from 40 to 70 mg. %, and in males from 48 to 75 mg. %. Approximately 80% of their cases of hepatitis or portal cirrhosis revealed a reduction in serum mucoproteins, in contrast to 125 patients with various forms of obstructive biliary tract disease, in whom only 2% demonstrated a serum mucoprotein reduction. The results of their investigations are indeed very impressive, demonstrating the value of mucoprotein determinations in patients where the differential diagnosis of jaundice is in doubt. The low serum mucoprotein values in our cases correctly indicated the intrahepatic nature of the jaundice. Although the mucoprotein value in case 2 was in the low normal range (50.0 mg.%), in the presence of jaundice this would favor the diagnosis of intrahepatic jaundice, since the mucoproteins are usually increased in the obstructive forms of jaundice.

Therapy

The management of cholangiolitic hepatitis, which is obviously medical, presents no difficult problem. The average case responds favorably to the usual regimen of bed-rest, proper high caloric diet and accessory vitamins. Some cases, however, show a tendency to a rather protracted course and, as Watson [1] has pointed out, to chronicity. The awareness of the existence of such potentialities in some cases would be a compelling reason for employing some therapeutic agent, such as ACTH, which may aid in altering or reversing the abnormal physiologic processes involved. As a rationale for the use of ACTH in this form of hepatitis, we must again refer to the possible analogy between the physiologic alterations in "cholangiolosis" and those occurring in nephrosis. The number of favorable reports [7, 8, 9] on the effect of ACTH in nephrosis and our own experience with corticotrophin in several cases of the nephrotic syndrome in adults leave no doubt as to its efficacy in some cases.

The use of ACTH and cortisone in hepatitis has also been reported by a number of investigators,[10, 11, 12, 13] and our failure to employ these agents in our cases was not due to an unawareness of their use but rather to the uncertainty of the diagnosis and preoccupation with extensive diagnostic procedures (as well as surgical exploration in case 2), a combination of circumstances depriving us of the opportunity to use them. The patients reported by Rifkin et al.[10] and by Evans et al.[11, 12, 13] did not have the pure cholangiolitic forms of hepatitis, such as we are reporting here; this is readily discernible from a review of their laboratory data. Nevertheless, it is reasonable to assume that even more favorable results may be anticipated from the use of ACTH in the form of hepatitis where the involvement appears to be limited to the cholangioli. The exact mode of action of the corticosteroids, either in nephrosis or in hepatitis, is mostly conjectural at this time, and various possibilities have been suggested. It is possible

that by effecting some readjustment of the protein and carbohydrate metabolism, these agents exert their favorable action on the tissues and, in the cases of cholangiolitis, where a state of increased permeability exists, render the cholangioli less permeable, thereby minimizing bile regurgitation. The observations of Evans et al.[11, 12, 13] of a dramatic fall in serum bilirubin with the institution of ACTH therapy would lend considerable support to the above contention. Whatever the actual explanation of its action may be, it is our opinion that, provided no individual, absolute contraindications exist, ACTH therapy in the cholangiolitic form of hepatitis deserves serious consideration.

Summary

Two cases of cholangiolitic hepatitis are reported, the diagnostic problems encountered are discussed, and the importance of a correct diagnosis and its therapeutic implications are emphasized.

The concept of increased permeability of the hepatic cholangioli as the cause of the regurgitation jaundice, suggested by Watson and Hoffbauer,[1] is reviewed, and additional factors lending support to such a concept are discussed. The term "cholangiolosis," analogous to the term "nephrosis," is suggested as indicating more clearly the physiopathologic alterations occurring in this form of hepatitis.

On the basis of the above concept, corticotropin therapy is suggested as a valuable adjunct in the management of this form of hepatitis, and the rationale for such therapy is discussed.

Summario in Interlingua

Le autores reporta duo casos del si-appellate "hepatitis cholangiolitic" e signala le difficile problema diagnostic que iste forma de hepatitis pote representar. Es sublineate le importante implicationes therapeutic de un correcte diagnose. Del puncto de vista clinic, hepatitis cholangiolitic presenta aspectos que a vices non differe del toto de illos de un ictero obstruente o del forma usual de hepatitis viral. Le differentiation diagnostic ab iste ultime entitate es fortemente suggerite per "dissociate" tests laboratorial del function hepatic. On trova hyperbilirubinemia, e hyperphosphatasemia de varie grados, sed omne le altere tests del functiones hepatocellular es normal. Le nivellos seral de mucoproteina in le casos hic reportate monstrava basse valores. Secundo le autores original, iste facto parla pro un diagnose de hepatitis e contra un diagnose de un forma obstruente de ictero. Biopsia hepatic es un importante adjuta diagnostic. Illo revela le presentia de thrombos biliari in le canaliculos hepatic (cholangiolos), producente lo que le pathologo appella "cholestase." Il ha nulle signos del usual alterationes pathologic que se incontra in hepatitis infectiose.

In lor discussion del concepto physiopathologic de hepatitis cholangiolitic, le autores se refere al theoria que un augmento del permeabilitate del cholangiolos hepatic produce un forma regurgitational de ictero como resultato de un effective exvasation de bile ex le canaliculos. Watson e Hoffbauer, le proponitores original de iste theoria, signala le facto que super le base del datos nunc disponibile il es plus logic supponer que le thrombos biliari (que es si characteristicamente presente in specimens bioptic) non es sufficientemente numerose pro causar extense obstructiones intrahepatic sed que lor presentia es un indication de exvasation de bile a transverso

le ledite parietes del cholangiolos. In iste processo relativemente plus aqua e minus substantia solide escappa verso le spatios de Disse, con le resultato que le bile remanente intra le capillares es spissificate e que assi le formation de thrombos biliari es promovite. Le alteration pathologic que resulta in un augmentate permeabilitate del parietes del cholangiolos es possibilemente analoge al lesion del tubulo renal que occurre in nephrosis. Le presente autores propone le adoption del termino "cholangiolosis" pro indicar plus specificamente le alteration anatomico-pathologic. Il es multo possibile que le concepto de "cholangiolosis" es de interesse non exclusivemente academic sed pote devenir importante pro le question del efficace therapia. De accordo con iste ideas le autores opina que ACTH deberea esser un therapeutico efficace in le forma cholangiolitic de hepatitis in tanto que illo reducerea le permeabilitate del canaliculos biliari e assi restaurarea lor function normal in un maniera simile al effecto de corticotrophina super le tubulos renal in nephrosis. Le autores se refere a plure previe reportos de frappante reductiones del bilirubina seral in consequentia del initiation de therapia a ACTH. Illes opina que iste reportos offere un forte supporto a lor assertiones tanto in re le concepto del physiopathologia de "hepatitis cholangiolitic" como etiam in re le argumentation in favor del uso de ACTH como un importante medication adjuncte in le tractamento de iste condition.

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AMEBOMA OF THE INTESTINE: AN ANALYSIS OF THE DISEASE AS PRESENTED IN 78 COLLECTED AND 41 PREVIOUSLY UNREPORTED CASES *

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AMEBOMA (amebic granuloma) is a localized thickening of the intestinal wall about an ulceration caused by *Endamoeba histolytica* which results in a lesion capable of being mistaken for a neoplasm because of the associated narrowing of the intestinal lumen and presence of a palpable mass.

In an attempt to clarify, if possible, this aspect of amebiasis, the literature has been reviewed and 78 reported cases of ameboma [1-53] have been selected for analysis and, in addition, 41 previously unreported cases of ameboma from my personal (5) and from the Armed Forces Institute of Pathology (AFIP) experience (36) have been studied. Criteria for inclusion in the analysis have been the presence of lesions which were localized and tumor-like in cases from which *E. histolytica* was isolated or the complement fixation test for amebiasis was positive. Excluded were cases in which the localized thickening appeared to result primarily from perforation and peri-intestinal abscess formation. Since the major clinical problem here lies in mistaking these lesions for tumor, they were included when the clinician in his gross description had carcinoma as his primary diagnosis even though the pathologist did not describe in detail the appearance of ameboma, or described a generalized disease of the intestine with a localized thickening. This involves three cases, two from the AFIP group and one from the collected group of cases. Reported cases in which no clinical or pathologic details are given were not included.

Marked thickening of the intestinal wall was described as having occurred in Lösch's [54] original case of amebiasis. Councilman and LaFleur,[55] who described the pathologic features of the disease so ably in 1891, stated: "The most striking characteristic in all [cases of amebiasis] and the one which first attracted our attention to this as a special anatomical form of dysentery was the great thickening of the intestine. Present in every case but more marked in some than others it sometimes involves all the coats, but in some cases is confined to the submucosal coat; and in every instance is more marked in this than the other coats." Indeed, their case VIII is undoubtedly one of multiple ameboma. Harris [56] (1898) stressed the difficulties in differentiating amebiasis from cancer, for which it might be mistaken. Kartulis [57] (1900) mentioned a case of amebiasis in which the intestinal wall was 225 mm. thick, and intestinal obstruction had occurred due to narrowing of the lumen. These earlier reports of the importance

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of intestinal thickening in amebiasis appear to have been overlooked generally until Lasnier,[58] Runyan and Herrick,[59] Yeomans,[2] Rogers [20] and Gunn and Howard [6] again emphasized these cases. With the advent of x-ray study of the intestine and its widespread employment, this condition is being reported with increasing frequency; indeed, Spicknall and Pierce,[26] who have recently reviewed the literature of this subject and added four

TABLE 1

Location of Ameboma in 119 Cases

Rectum	48
Cecum	43
Transverse colon	18
Sigmoid colon	11
Ascending colon	11
Descending colon	6
Multiple sites	15

cases of their own, report finding 195 cases. However, they have included cases without supporting detail and many cases in which apparent therapeutic response to various antiamebic drugs was the diagnostic criterion.

The pathology of this phase of amebiasis is essentially an exaggeration of the basic lesion of the chronic disease, namely, development of fibroblastic proliferation, edema and round cell infiltration, mostly in the submucosa but also in the muscularis, and particularly in the subserosal coats of the base

TABLE 2

Complications in 119 Cases of Ameboma

Intestinal obstruction—intermittent	12	
complete	19	
Total		31
Amebiasis cutis		16
Liver abscess		14
Perforation		9
Peritonitis without gross perforation		9
Intussusception		7
Lung abscess		5
Pleurisy		4
Jaundice		3
Granulomatous seeding of peritoneum		2
Fecal fistula		2
Fatal hemorrhage		2
Perianal abscess		1
Volvulus		1
Pericarditis		1
Waterhouse-Friderichsen syndrome		2
Ureteral obstruction		1

and surrounding area of large ulcerations or multiple smaller ulcerations so situated as to occupy all or a major part of the circumference of the intestine. An added tumor-like characteristic of amebiasis is the development of large mucosal sloughs which hang in the intestinal lumen as filling defects. It is this last feature of the disease which results in the occasional rapid disappearance of the filling defect without treatment. The location

TABLE 3

Associated Conditions in 119 Cases of Ameboma

Adenomatous polyp of intestine	5
Cirrhosis	1
Carcinoma of bile ducts	1
Calcification at site of treated liver abscess	2
Infectious hepatitis	1

of these lesions (table 1) is essentially the same as those of amebic lesions in general.

Complications are shown in table 2 and are quite similar to those encountered in amebiasis without ameboma,[60] with the exception that the incidence of peritonitis and perforation is less, due to exclusion of those cases in which peri-intestinal abscess appeared to be involved in the thickening of the intestinal wall. Also amebiasis cutis occurs much more frequently in this group of cases. Intestinal obstruction, either partial or complete, occurred in 31 of these cases. Intussusception occurred in seven and volvulus in one of these. The ameboma was multiple in 15 cases.

In the 92 cases in which age and sex were mentioned, 84 were males and eight females. Only 1 patient was less than 20 years old, 47 were in the 20 to 40 age group, 41 in the 40 to 60 age group, and only three were older than 60. The symptoms in some of the collected and AFIP group of cases were recorded in a sketchy manner; however, the record was explicit in enough cases that the pattern of symptomatology is clearly evident. Diarrhea, usually intermittent and often bloody, and lower abdominal cramps were the most frequently recorded symptoms (table 4). In seven of these cases amebiasis had been known to be present for 15 or more years. Body temperature was mentioned in only 34 of the reports studied, and fever, usually low grade, was present in all but two of these cases. An intestinal obstruction syndrome was present in 31 of the cases. An interesting situation revealed by this study was the occurrence during antiamebic therapy of intestinal obstruction in six and the appearance of the mass in 12 of the cases studied. Loss of weight was specifically noted in 33 cases; this varied from five to 50 pounds. In many other cases the course of the disease was such that loss of weight very likely was present but not recorded.

The most commonly mentioned physical finding was the presence of an abdominal or rectal mass (77 cases). This was described as tender in the majority of the cases. In addition, abdominal tenderness was stated or

TABLE 4

Symptoms of 119 Cases of Ameboma

	Present	Not Mentioned	Absent
Diarrhea	84	34	1
Lower abdominal cramps	76	43	0
Fever	33	84	2
Loss of weight	33	86	0
Intestinal obstruction syndrome	31		88

implied to be present in 44 cases. Hepatomegaly was mentioned as present in 15 cases (table 5).

In 72 cases barium enema x-ray examination was not mentioned as having been performed. In 42 cases the examination was positive and in five additional it was equivocal. Positive findings were recorded as filling defects ordinarily, and equivocal findings as spasm of a localized area of the

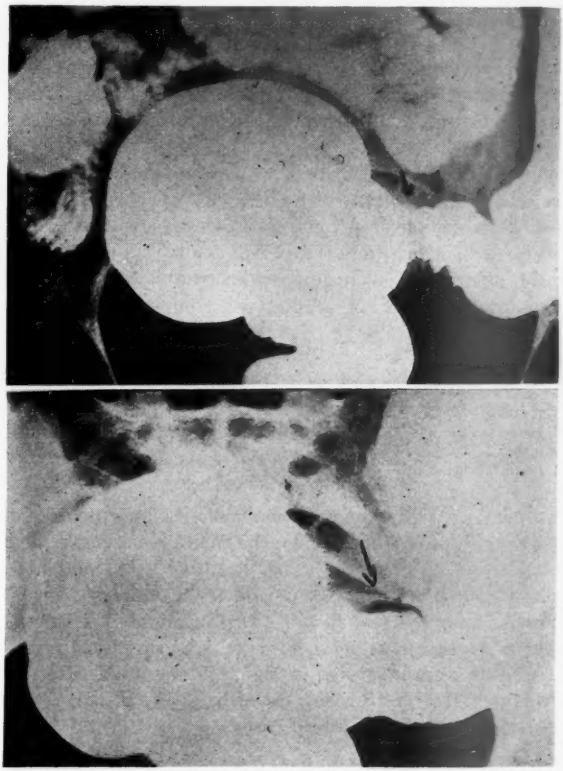

FIG. 1. Ameboma of the sigmoid colon. *Above,* before treatment; *below,* after treatment. Note the minute serrations in the "before treatment" x-ray picture. (X-Ray Department, Tokyo Army Hospital.)

intestine. These were most often interpreted as evidence of malignancy, even in one case in which three filling defects were observed. In the barium enema examination of one of my personal cases (figure 1), the serrations clearly to be seen in the "before treatment" view of the lesion were also to be observed in the illustrations of 15 of the reports in the literature. My

TABLE 5

Physical Findings in 119 Cases of Ameboma

	Present	Not Mentioned	Absent
Palpable mass	77	42	0
Ulcers or mass on sigmoidoscopic examination	44	65	10
Abdominal tenderness	44	75	0
Amebiasis cutis	16	0	103
Hepatomegaly	15	102	2

attention was called to the occurrence of these minute lesions in the barium enema x-ray of amebiasis by my colleague, Lt. Colonel Harold Vinson.[61] Attention to this feature of the intestinal x-ray of amebiasis was also called by Henderson.[62]

Leukocytosis, usually mild in degree, was present in 27 of the 42 cases in which the white blood count was mentioned; however, it exceeded 40,000 in two cases, both complicated by liver abscess. Anemia was present in 21 of the 30 cases in which the erythrocyte count was mentioned (table 6).

One of the criteria for inclusion in this study was the recovery of *E. histolytica* or the presence of a positive complement fixation test for

TABLE 6

Laboratory Findings in 119 Cases of Ameboma

	Present	Not Mentioned	Negative
Leukocytosis	29	73	17
Anemia	21	88	10
Barium enema	47	72	0

amebiasis (table 7). Only one case was included in which the complement fixation test was positive but in which amebas were not demonstrated. Stools were positive in 59 of the cases, negative in 12 and not mentioned in 47 cases. In some of the cases in which the stool was negative, many stools had been examined (24 in one case). Sigmoidoscopic examination was positive in 43 cases, negative in nine, and not mentioned in the remainder. Amebas were identified in biopsy tissue in 27 cases, and this examination was negative in 18 cases. Amebas were discovered for the first time in the postmortem tissues in 30 cases.

TABLE 7

Data on Isolation of *E. histolytica* from 119 Cases of Ameboma

	Amebas Found	Negative	Not Mentioned
Stool	59	12	48
Biopsy specimen	27	18	74
Sigmoidoscopic specimen:			
Smear	12		
Biopsy	12		
Only at autopsy	27		
Only at recheck of autopsy	3		

In one case complement fixation test alone was positive.

Forty-one of these patients died. Of these, only eight had received antiamebic therapy. In six of the collected group and eight of the AFIP group of cases the recorded follow-up was inadequate to determine the outcome of the case. In the AFIP group of cases this inadequacy resulted from the diagnosis being established from a surgical specimen. Operations were performed on 52 of these patients, and in 10 of these the outcome could not be determined due to insufficient reporting of follow-up. *In the 42 cases in which outcome was reported 26 patients died.*

TABLE 8

Treatment of Ameboma in 52 Cases

Emetine alone	15
Emetine in combination	20
Chloroquine in combination	5
Antibiotic alone	1
Antibiotic in combination	4
Carbarsone alone	1
Arsenic in combination	23
Diodoquin alone	2
Iodide in combination	9
Atabrine in combination	5

The type of antiamebic treatment the 52 cases received in which it was recorded is shown in table 8. The therapy is unknown in 34 cases either because the amebacidal agent was not stated (20) or because the recorded follow-up was inadequate (14). An additional 33 patients died untreated. Two of these collapsed and died following rectal biopsy and were found to have edema and/or hemorrhage of the adrenal cortex (Waterhouse-Friderichsen syndrome). In the 52 treated cases emetine alone (15) or in combination (20) was the agent most often employed. In 11 of these

TABLE 9

Type of Antiamebic Therapy in 8 Fatal Cases of Ameboma

Emetine	1
Emetine, Carbarsone and chiniofon enemas	1
Emetine, Carbarsone, Diodoquin	1
Emetine, neoarsphenamine	1
Aureomycin, Carbarsone	1
Aureomycin, chloroquine	1
Not mentioned	2

prolonged therapy was necessary, and in five the stools remained positive for *E. histolytica* in spite of massive emetine therapy and improvement in clinical condition. For example, Gunn and Howard's case 1 took "hundreds of emetine injections" and developed ameboma in the face of this therapy. Palmer's patient was hospitalized nearly two years, and Nushan and Miller's patient for 278 days. The antiamebic therapy employed in the eight fatal cases which received such therapy is recorded in table 9. Four of these cases were treated with emetine alone or in combination. In two of these from the AFIP group of cases death occurred after four courses of antiamebic

therapy consisting of emetine in combination with iodides and arsenic compounds, and amebas were still to be seen in the tissues. One of these cases had atabrine coloration of subcutaneous tissues due to suppressive malarial therapy. Five patients were treated with antibiotic alone or in combination, and two of these, who were treated with Aureomycin in combination, died. One patient, not included as treated with antibiotics because of inadequate follow-up, was prepared for surgery with "massive Aureomycin" therapy, and motile trophozoites of *E. histolytica* were present in the intestinal ulcers removed at surgery. One of these patients in whom Aureomycin was combined with Carbarsone died in collapse and, in addition to the ameboma in the rectum, the upper colon and small intestine presented a postmortem appearance compatible with pseudomembranous enterocolitis, which has been described as a complication of antibiotic therapy.[63] Chloroquine was employed alone or in combination in five patients, one of whom died. Five patients were treated with atabrine and Carbarsone in combination.[64] In all five the lesions disappeared and the aspirations were negative for *E. histolytica* at two follow-up sigmoidoscopic examinations. One patient in whom the rectal granulomatous lesion disappeared completely and numerous stools and the specimens secured at five sigmoidoscopic examinations were negative for amebas had evidence of continued disease resembling idiopathic thrombo-ulcerative colitis. He was treated with a course of emetine of 10 daily 1-gr. injections and 10 days of Terramycin, 1 gm. daily, without amelioration of the clinical picture. He was then given intravenous ACTH, with dramatic improvement in his clinical picture and improvement of his intestinal lesions. He was evacuated at this point. Late follow-up indicates that he continued to improve. One other case received ACTH in addition to antiamebic therapy. In one case radium was employed in the mistaken idea that the mass was carcinoma and the mass disappeared. A further case, not recorded in those analyzed due to inadequate clinical data, was reported by Druckmann and Schorr [65] as having been treated by x-ray, with disappearance of the mass. In five cases (two of which had colostomy) the mass disappeared without antiamebic therapy but amebiasis was still present.

In the review of the literature of this subject a number of cases were encountered which did not fit the criteria for inclusion in the study group of cases, usually because it was not clear whether *E. histolytica* had been found in the case, or other essential data regarding the case were lacking. For example, Rogers, in describing two cases of ameboma treated with emetine which were included in the study, also mentioned that he had seen 13 such cases previously, with 11 deaths, but gave no data regarding isolation of the causative organism, location of the lesion or type of therapy employed. The first recorded case of ameboma, case 8 of Councilman and LaFleur, was not included because diagnostic and treatment technics which were desired to be evaluated were not available at the time the case was described,

nor was the location of the lesions stated. Christopher's [66] often quoted case of rectal stricture due to amebiasis had a similar stenosis over much of the colon and was not included for that reason. No case was included in which *E. histolytica* or a positive complement fixation test for amebiasis was not demonstrated. For example, a case from my personal experience was excluded in which a mass 5 by 7 cm. was present on the left lateral wall of the rectum 10 cm. from the anal orifice. The patient also had associated liver abscess with pleuropulmonary involvement.[67] Typical amebic miliary abscesses were to be seen surrounding the mass, which had several centimeter-sized superficial ulcerations upon it. Amebas were not seen, possibly due to his having previously received several days of Aureomycin therapy; because of his critical clinical condition antiamebic therapy was started. The rectal mass, pleural effusion and liver signs cleared up completely during 30 days of Atabrine and 10 days of Carbarsone therapy. Also not included were three AFIP cases in which amebas were not definitely identified in the tissues, one because a microtome was not available, one because postmortem autolysis had occurred and, while organisms having the appearance of *E. histolytica* were seen, definite identification was impossible; the third received antiamebic therapy ante mortem. Other cases which appear clinically identical have been described in the literature as nonspecific granulomatous or ligneous lesions of the large intestine.[68-71]

Discussion

To reach a better understanding of that feature of amebiasis which Ochsner and DeBakey [8] termed ameboma, 78 cases collected from the literature and 41 previously unreported cases have been analyzed. Noteworthy is the ponderous chronicity of amebiasis with severe exacerbations and often spontaneous remission that is exhibited by these cases. Harris [56] emphasized this feature of the disease when he stated in 1898, "In no other disease can death be approached so closely and recovery follow." These cases demonstrate clearly the pitfalls to be expected in evaluating therapeutic technics in amebiasis. A mortality of 41 cases out of 105 in which follow-up was adequate underlines the truth of Harris' dictum in 1898 that amebiasis "is a very fatal disease."

Tumor-like thickening of the intestine appearing during the course of chronic amebiasis has been recognized as occurring as long as amebiasis itself has been known. Of considerable interest is the fact that Annesley's [72] pathologic illustrations of some of the dysentery cases which he saw in India (1828) portray thickened intestinal wall and adhesions to surrounding intra-abdominal structures. The strange thing is that this feature of the disease has been so little appreciated by clinicians as to be reported as a new feature of the disease by more recent observers from time to time.

The pathology of this condition is clearly that of amebiasis, with the added feature that in these cases the ulcerative lesion is large, or multiple

ulcers are close together. The thickening that causes the most minute miliary abscess of amebiasis to protrude into the intestinal lumen is in these cases proportionately greater and the surrounding undermined mucosa overlying the summit of the lesion contributes greatly to the space-occupying feature of the lesion. Apparently in rare instances the mucosa was successful in reëstablishing itself over the defect leaving the lesion confined to the submucosa. This appears to account for the rare case of recorded stricture which disappears with successful therapy. More frequently, mucosal sloughs of large size are formed by the undermining so characteristic of amebiasis; this is particularly likely to occur when small lesions adjacent to each other burrow together beneath the mucosa and in some instances compromise its blood supply. The most able descriptions of the pathologic features of this condition are found in the papers of Councilman and LaFleur,[55] Gunn and Howard [6] and Ernst.[46]

My study of this condition has emphasized the frequent occurrence of eosinophils in the cellular infiltrate, which is customarily quite sparse and made up of lymphocytes, leukocytes, plasma cells, histiocytes and often foreign body giant cells. This, together with edema, hyaline deposit and fibroblastic proliferation, makes a quite characteristic picture. An added feature is the location of the amebas beyond the area of maximal tissue change, and their sparse occurrence or often apparent absence in the areas of the lesion that are most dramatic. This appears to be the explanation of the finding of 18 negative biopsies out of 45 cases, and the fact that in three of 30 autopsies recorded in the study group the etiologic agent was found only on review of the material by a second pathologist.

The unusual incidence of amebiasis cutis in this group resulted from the occurrence of that complication about a colostomy orifice or in an abdominal incision, although perianal involvement occurred in five of the 16 cases with this complication. Liver abscess and peritonitis are less frequent in this group of cases than in amebiasis in general. The possibility exists that liver abscess was present and not recognized in some of those cases which were treated and recovered, since the finding of an unsuspected amebic liver abscess at autopsy examination occurs not infrequently. The incidence of peritonitis and perforation is less because this is a selected group from which perforation or peritonitis occurring prior to appearance of the mass was excluded. In addition, it appears that there are two major pathologic forms which amebiasis may take—one, the hyperplastic form under consideration here, the other, primarily a necrotizing process in which perforation, often multiple, is the usual result. Apparently perforation occurs more rarely in the hyperplastic form and is then not infrequently a manifestation of circulatory impairment due to intestinal obstruction. An unusual complication described as occurring in a case of rectal ameboma reported by Freedman and Cleve [48] was seeding of the peritoneum with numerous small nodules. These had the gross appearance of tumor im-

plants. I have been informed by the surgeon who operated upon this case, Colonel Joseph P. Russell,[78] that biopsy of one of these nodules revealed granulation tissue, but no amebas were seen. A subsequent follow-up from the hospital to which the patient was evacuated revealed that upon re-operation there the rectal mass and the peritoneal granulations had disappeared. One case studied at AFIP had a similar seeding of the peritoneum with small granulomata. Amebas were seen in some of these.

Associated conditions (table 3) are the same as those previously recorded for amebiasis in general, except that no intestinal carcinoma was included in this group, although two cases were studied in the AFIP group in which ameboma was associated with carcinoma of the large intestine; but these cases were excluded from the study group because the symptoms in both of them appeared to be clearly due to the cancer, the ameboma having been a small part of the clinical picture. Spicknall and Pierce report that they found 31 cases recorded in the literature in which carcinoma of the large intestine either accompanied or followed amebiasis. The formation of adenomatous polyps at the site of amebic ulcerations has previously been stressed. The occurrence of these tumors in five of the present group of cases underlines this sequel to amebic ulceration. Adenomatous polyps have been found associated with 7% of cases of amebiasis at Fort Knox,[74] and with 9% (in two successive years) at Tokyo.[75, 76] The increased incidence of cirrhosis in cases of chronic amebiasis coming to autopsy examination was not apparent in this group of cases, suggesting that the hyperplastic form under consideration here is less productive of that condition. One case of carcinoma of the liver found in the AFIP group of cases suggests that the same irritative process that leads to adenomatous polyps and carcinoma in the intestine may operate in the liver as well.

The clinical picture of this type of amebiasis appears to be identical with that of chronic amebiasis in general.[74] In other words, these patients had intermittent diarrhea, lower abdominal cramps, low grade fever, malaise and loss of weight. The diarrhea was often recorded as bloody. In addition, one third of them had an intestinal obstruction syndrome, either intermittent or complete. The occurrence of amebiasis cutis as a complication of surgery or perianally is an unusual feature of this form of amebiasis. It was recorded with striking frequency that the skin involvement was associated with severe pain and excruciating tenderness. The frequent finding of tenderness over the large intestine in this group of cases is comparable to that observed in colonic amebic infection in general; however, the presence of a palpable mass in the majority of these patients sets ameboma aside as a special form of the disease. Often the mass was recorded as tender and movable, and not infrequently the description of the mass was "sausage-like." Tenderness elsewhere over the intestine or the liver was sometimes recorded.

The x-ray appearance of ameboma has been described by a number of

observers, and the criteria for differentiating this lesion from carcinoma have been listed by Druckmann and Schorr [65] as follows:

1. Greater length of ameboma.
2. Multiplicity of lesions in ameboma.
3. Relative incompleteness of stenosis in ameboma.
4. Less pain on passage of barium past ameboma.
5. Gradual transition from normal to involved intestine in ameboma.
6. Difference in caliber of stenotic lesion in ameboma.
7. More or less regularity of mucosal relief in involved area in ameboma.
8. Disappearance of lesion after vigorous antiamebic therapy.

To this I would add the appearance of serrations in the amebic case, as mentioned above, and point out that the minute lesions represented by the serration need not be immediately adjacent to the large filling defect being studied. I would emphasize the point which Bell [77] made in discussing this problem, namely, that often the cecal signs of amebiasis are present when the filling defect is elsewhere. It is well to recall that antiamebic therapy does not result in rapid disappearance of the mass in all instances; indeed, in some recorded cases the mass appeared during such therapy.

It is apparent from this study that the diagnosis of amebiasis is often missed, since 30 of the patients with fatal disease were not diagnosed until postmortem examination, and three additional such cases were diagnosed so late in the course of the disease that treatment could not be applied. A number of nonfatal cases were diagnosed only after amebiasis cutis appeared. Analysis of the data leads me to the conclusion that many other fatal cases are missed either because postmortem examination is not done or because the examining pathologist is not alert to the picture which this disease presents. For example, the correct diagnosis was established in three of these cases only on review of the original pathologist's tissues and report. Some of the cases reported by Moynihan [68] and Ginzburg and Oppenheimer [69] as nonspecific granuloma of the intestine appear to be excellent examples of this disease. It is likely that some of the cases described by Bargen and Jacobs [70] and Walters and Synhorst [71] as ligneous typhlitis are also examples of this disease.

Coming as they do from all over the world, the cases in the present group serve to emphasize again that amebiasis is not a disease of the tropics and far corners of the earth, but is ubiquitous and must be thought of or diagnosis cannot be established. If one assumes that lack of mention of stool, sigmoidoscopic examination and biopsy examination in the protocol of a report of a case of amebiasis indicates that the examination was not performed, then one is forced to the conclusion from the data presented above that these cases have been very inadequately studied from the diagnostic point of view, since stool, sigmoidoscopic and biopsy examinations were not mentioned in 48, 67 and 74 cases, respectively. The importance of employ-

ment of every diagnostic technic for demonstration of *E. histolytica* is adequately emphasized by this group of patients. In one case 24 stools were examined and found negative, in another 12 were examined and found negative before a single positive examination was reported. In two cases amebas were demonstrated by culture. The value of sigmoidoscopic examination in diagnosis of this disease is apparent when it is realized that, of 54 such examinations performed, evidence of the nature of the disease process was secured in 44. Clearly a neglected instrumentality in the study of this disease is the examination of aspirated specimens secured through the sigmoidoscope, since the organism was identified in this way in only 12 of these 54 cases. In many of the others no mention was made of a search for *E. histolytica*, even though ulcers were reported as visualized. Biopsy of lesions through the sigmoidoscope established the diagnosis in 12 of these cases. The nature of the pathologic process is such that biopsy must be taken from the ulcerative base of the lesion to demonstrate the etiologic agent. The negative biopsies reported probably reflect inadequate specimens and, in addition, reflect a lack of appreciation of amebiasis on the part of the pathologist in some instances. In reviewing nine autopsy cases diagnosed as nonspecific enterocolitis from a busy laboratory, I found that special stains for *E. histolytica* had been employed in only three.

The fatality-producing impetus given this disease by surgery is emphasized in this group of cases, in which 26 patients died out of 42 operated upon in whom follow-up report was adequate. It would appear that a repetition of diagnostic points previously made would be desirable to prevent cases of this disease from coming to surgery unnecessarily. *E. histolytica* must be searched for by every possible diagnostic technic if these fatalities are to be prevented. Thus direct smears from fresh specimens (within 30 minutes) must be examined; stained smears and concentration specimens [78] for cysts must be examined on this same specimen. Cultures for *E. histolytica* must be made of these specimens. Direct and stained smears of material aspirated during sigmoidoscopic examination must be examined and cultures made of this material. Saline purge, preferably sodium phosphate in dose adequate to result in three liquid stools, with immediate search of each of the liquid specimens for trophozoites, often results in isolation of the organisms when other means fail. If the patient's condition is precarious, sigmoidoscopic examination with demonstration of lesions compatible with amebiasis will result in strong presumptive evidence for that diagnosis, and furnish fresh specimens for search for *E. histolytica* without delay. Antibiotic medication, barium enema or barium by mouth, bismuth and drastic purge all make demonstration of *E. histolytica* more difficult for the succeeding 10 days. It is my belief that a clinical diagnosis is justified in some cases of this disease; this is borne out by the previously cited critically ill case of ameboma with liver abscess and pleuropulmonary involvement not included in the study group of cases who had received

Aureomycin. This case, as well as many cited in the literature but not included in the study group of cases, had a favorable outcome based upon antiamebic therapy given upon a clinical diagnosis.

No treatment of amebiasis presently available is completely satisfactory. If this type of amebiasis is considered to be the severest test of antiamebic effect, it would appear that Atabrine combined with Carbarsone is the best therapy presently available, since all five of the cases included in the study group, plus the one not included, had a prompt recovery from the granuloma within 30 days. The nature of the continued illness of the case cited which apparently responded to ACTH is unclear. Kirsner and Palmer [79] have reported the occurrence of idiopathic thrombo-ulcerative colitis as a sequel of amebic infection, and it is possible that this case is such a one. Certainly a determined effort to demonstrate *E. histolytica* by smear, culture and concentration technics was unsuccessful, and the lesions remaining in the intestine did not grossly resemble those of amebiasis.

It is my belief that treatment of amebiasis with emetine should be abandoned. Craig,[80] Mühlens and Menk,[81] Wilmot et al.[82] and Hargreaves,[87] among others, have emphasized its therapeutic inefficiency. The present group of cases in which prolonged therapy (31% of cases treated with emetine), often unsuccessful in the sense of eradication of the organism (15% of cases treated with emetine), combined with the morbidity [83] and mortality from its employment, emphasizes emetine inadequacies. Two cases of fatal emetine toxicity were discovered in this present review of the data at AFIP, in addition to those previously reported by others.[84–87] In addition, reference to table 8 reveals the fact that four of the eight fatal treated cases were treated with emetine, two of whom died after four courses of emetine. One of my personal cases had received seven courses of emetine, usually with relief from his diarrhea of only a week or less. His granuloma and symptoms were cleared after 30 days of Atabrine and 10 days of Carbarsone therapy.

Antibiotic therapy [88–89] appears to be useful predominantly as an adjunct to other antiamebic therapy. The present group of cases contained two antibiotic-treated cases in the eight fatal treated cases. The occurrence of pseudomembranous enterocolitis in one of these illustrates a potential danger in antibiotic therapy that should not lightly be dismissed. It should be remembered that the cases of pseudomembranous enterocolitis which were described prior to antibiotic therapy availability were often ones in which obstructive types of lesions of the intestine were present.[90] One case treated with Fumidil had a mass due to amebiasis a month later.

This group of cases reëmphasizes the dangers inherent in operating upon amebiasis which is untreated, having as it did a mortality of 26 out of 42 cases operated upon in whom the postoperative course was adequately reported. In addition, the two cases who collapsed and died following rectal biopsy must be thought of as having surgery as a contributing factor.

These are not included in the 26 cases because of the minor nature of the surgery. Cases were often encountered where death occurred soon after surgery was performed. This appears to justify the recommendation that every intestinal mass should have antiamebic therapy preoperatively if the possibility exists that the lesion is inflammatory, and operation should be postponed if treatment response is present. It should not be forgotten that amebiasis and cancer may coexist in the patient,[91, 92] and while a delay of 15 days for antiamebic therapy appears completely justifiable, surgery should be done if the response of the mass to therapy is not definite. The appearance of a skin infection about an incision after intestinal surgery should arouse one's diagnostic suspicion of amebiasis. A number of the cases in the study group were not diagnosed until the amebiasis cutis was widespread and unresponsive to all antibacterial therapy. The occurrence of intestinal obstruction in six cases and appearance of the mass during antiamebic therapy in 12 cases are probably the result of edema and swelling about the lesions due to a Herxheimer reaction. As previously reported, this type of reaction appears during antiamebic therapy in about one third of cases treated.[89]

Summary

Analysis of data from 119 cases of ameboma collected from the literature and from personal and AFIP experience has been presented. This manifestation of amebic infection has been known from the earliest recorded cases. The pathology of this condition is essentially an exaggeration of the basic lesion of amebiasis, and results mainly from thickening about a large ulceration or several closely grouped smaller ones. Complications are similar to those of amebiasis in general, except that intestinal obstruction and amebiasis cutis occurred more frequently in this group of cases, and peritonitis, perforation and liver abscess less frequently. The hypothesis is advanced that pathologically amebic infection may take a necrotizing form or a hyperplastic form, and that these present cases are a manifestation of the hyperplastic form. With the exception that palpable abdominal mass was often present, the symptoms and physical findings of these cases appear identical with those of amebiasis in general. These consist in diarrhea, usually bloody, lower abdominal cramps, loss of weight, mild fever and abdominal tenderness. An additional exceptional feature of this form of amebiasis is the frequency with which the intestinal obstruction syndrome was encountered. Leukocytosis and anemia were present in some cases. Barium enema examination reveals a filling defect with some distinctive features, which are summarized, and the presence of serrations about these defects is emphasized as a diagnostic point. Since the diagnosis was established at postmortem examination in 30 of these cases, and in three additional was established only when the patient was moribund, emphasis has been put upon the diagnostic technics. Analysis of the methods employed to demonstrate *E. histolytica* showed that no single diagnostic technic

could be relied upon to the exclusion of others. Methods found by us to be useful in demonstrating the presence of this organism are reviewed, and especial emphasis is placed upon the benefits to be derived from sigmoidoscopic examination of patients suspected of this disease.

Mortality in this group of cases was 40%. Treatment technics are analyzed, and the superiority of combined Atabrine-Carbarsone therapy is pointed out. It is suggested that the therapy of amebiasis with emetine be abandoned because of its toxicity and demonstrated inefficiency in this group of cases. Surgery in amebiasis is reëmphasized as a dangerous procedure by this analysis, since 26 died out of 42 cases operated upon, and an additional two cases died after rectal biopsy. It is suggested that, when an abdominal mass is suspected of being inflammatory, every diagnostic effort be made to establish the etiologic agent, and if that is not possible, antiamebic therapy with Atabrine and Carbarsone be given on clinical grounds, particularly if sigmoidoscopic examination reveals the presence of lesions compatible with amebiasis. Emphasis is laid upon the reverse of this medal, namely, that patients with carcinoma of the intestine may also have amebiasis, particularly since there appears to be a definite connection between amebiasis and adenomatous polyps of the large intestine.[93] The appearance of abdominal mass and/or intestinal obstruction during antiamebic therapy in some of these cases is suggested as being a manifestation of Herxheimer's reaction.

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SUMMARIO IN INTERLINGUA

Es presentate un analyse del datos de 119 casos de ameboma colligite ab le litteratura e ab experientias del autor e del Instituto Pathologic del Fortias Armate. Iste typo de manifestation de infectiones amebic ha essite cognoscite ab le tempore del prime casos describite. Le pathologia de iste condition es in essentia un exaggeration del lesion fundamental de amebiasis e resulta principalmente del spissification in le region circa un large ulceration o circa plure parve ulcerationes occurrente in un gruppo restringite. Le complicationes es simile al complicationes de amebiasis in general, excepte que le presente gruppo de casos monstrava un plus alte frequentia de obstruction intestinal e de amebiasis cutanee e un plus basse frequentia de peritonitis, perforation, e abscesso hepatic. Es postulate le hypothese que ab le puncto de vista pathologic infectiones amebic pote prender un forma necrotisante o un forma hyperplastic e que le presente casos es manifestationes del forma hyperplastic. Con le exception del facto que palpabile massas abdominal esseva frequente, le symptomas e le constatationes physic in le presente casos appareva identic con illos de amebiasis in general. Istos consiste de diarrhea (usualmente sanguinee), crampos infero-abdominal, perdita de peso, leve grados de febre, e sensibilitate abdominal sub pression. Un altere characteristica exceptional del presente forma de amebiasis es le frequentia del syndrome de obstruction intestinal. Leucocytosis e anemia esseva presente in alicun casos. Clysteres a barium revelava un defecto de plenation con certe tractos distinctive (que es summarisate). Le presentia de serrationes circa le loco de iste

defecto es sublineate como un puncto de importantia diagnostic. Proque le diagnose esseva establite in 30 del presente casos solmente al examine autoptic e in tres casos additional solmente quando le patiente esseva moribunde, nos presta attention special al technicas diagnostic. Un analyse del methodos usate pro demonstrar *Endamoeba histolytica* indica que nulle technica diagnostic individual pote servir satisfactorimente in omne casos. Nos presenta un revista del methodos que nos trovava utile in demonstrar le presentia del organismo mentionate. Es sublineate specialmente le beneficios obtenibile ab le examine sigmoidoscopic de patientes suspecte de haber iste morbo. Le mortalitate in le gruppo hic reportate esseva 40 pro cento. Es analysate le technicas therapeutic. In isto nos signala le superioritate de un therapia combinate a Atabrina e carbarsona. Nos propone que le tractamento de amebiasis con emetina sia abandonate a causa de su toxicitate e su demonstrate inefficacia in le presente gruppo de casos. Es sublineate de novo per le presente analyse que interventiones chirurgic in amebiasis es periculose. Ex le 42 casos operate, 26 esseva mortal. Duo patientes additional moriva post biopsia rectal. Nos recommenda que in casos del suspicite presentia de inflammatori massas abdominal, omne effortio diagnostic es facite pro identificar le agente etiologic, e si isto non es possibile, que un therapia antiamebic con Atabrina e carbarsona es initiate super le base del constatationes clinic, specialmente si le examine sigmoidoscopic revela le presentia de lesiones compatibile con amebiasis. Nos sublinea le reverso del medallia: le facto que patientes con carcinoma del intestino pote haber in plus amebiasis, specialmente proque il pare que un connexion existe inter amebiasis e polypos adenomatose del intestino crasse. Nos opina que le apparition de massas abdominal e/o obstructiones intestinal durante le therapia antiamebic es a vices un manifestation del reaction de Herxheimer.

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COMPLICATIONS FOLLOWING SUBTOTAL GASTRECTOMY FOR PEPTIC ULCER*

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PURPOSE OF STUDY

THE purpose of the clinical appraisal was to ascertain, if possible, the features existent in nonoperated peptic ulcer case that may predispose to postgastrectomy complications.

It was also felt that some pattern might be forthcoming to serve as a guide in determining the likelihood of postoperative symptoms.

PLAN AND MATERIAL OF STUDY

One hundred four cases that had undergone subtotal gastrectomy for peptic ulcer during the last five years have been reviewed and evaluated as to the incidence of postgastrectomy complications.

Of these 104 cases, follow-up studies were carried out on 74, the period of follow-up averaging 14.7 months, with a range of 0 to 67 months after

TABLE 1

Dumping syndrome		10
Uncomplicated	6	
Intestinal adhesions and homologous serum jaundice	1	
With anemia	1	
With hemorrhage	2	
Stomal ulcers		5
Uncomplicated	1	
With hemorrhage	3	
With perforation	1	
Mobility disturbance (disorder)		1
Hematemesis and melena (site?)		1
Psychophysiologic gastrointestinal disturbance		4
Anemia (gross deficiency)		2
Homologous serum jaundice		5
Died		3
Incisional hernia		3
Duodenal fistula		1
Intestinal adhesions with obstruction		1
Total		36

operation. The very few patients who had zero months' follow-up were those who died during operation or very shortly postoperatively. The remainder had a minimum of two months' follow-up.

Of the 74 patients, 36 were found postoperatively to have experienced one or more complications which could be attributed to the operative procedure.

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TABLE 2
Mortality Rate with Gastrectomy

Author	Year	No. of Cases	Per Cent
Walters et al.	1939	215	2.8
Lake	1948	615	5.7
Penick	1949	850	3.7
Eastman	1949	114	5.2
McGuire VAH	1954	104	2.9

It should be pointed out that the 36 patients with complications were followed for an average of 16.8 months, in spite of the inclusion of the fatal cases, whereas the uncomplicated group of 38 patients was followed for an average of 12.4 months.

Complications: The types of postgastrectomy complications encountered are listed in table 1. These complications totaled 43 among the 36 patients.

Mortality Rates: A review of the literature reveals that there has been a progressive decline in the mortality rate from gastrectomy over the past 25 years, to a range of between 2 and 8% during the last decade. Representative rates are shown in table 2, together with our rate of 2.9% (three cases) in this study.

TABLE 3
Complications with Relation to Age

	Average Age	Range
Dumping syndrome	43	21–75
Stomal ulcers	39	25–60
Hemorrhage	37	25–60
Anemia	50	34–62

Age at Operation: The average age at operation was 45.0 years, with a range of 21 to 75 years. The complicated cases showed an average age of 45.3 years, with the same age range, i.e., both the oldest and the youngest members of the study experienced postoperative complications.

Complications With Relation to Age: A study of the ages of those patients with complications is noted in table 3. The number of cases is so small and the age range so broad that it is felt age cannot be implicated as a primary factor in the production of the postoperative complications in this study.

Relationship of Race to Complications: No significant relationship could be observed between the race of those patients receiving subtotal gastrectomies and the incidence of complications postoperatively, as is readily seen in table 4.

TABLE 4
Relationship of Race to Complications

	Uncomplicated	Complicated
White	58	31
Negro	10	5

Ulcer Site With Relation to Complications: Of the gastrectomized peptic ulcer cases, there were 69 duodenal ulcers, 34 gastric ulcers and one undetermined site, i.e., a ratio of approximately two duodenal ulcers to one gastric ulcer. Of these numbers, 24 duodenal ulcers and 11 gastric ulcers became complicated postoperatively, and thus maintained a ratio of two to one in the complicated group (table 5).

The incidence of the "dumping syndrome" in relation to the two sites of ulceration shows five cases occurring in each of the duodenal and gastric ulcer groups. However, since twice as many duodenal ulcers as gastric

TABLE 5

Sites of Ulcers

	Duodenal	Gastric	Undetermined
Total	69	34	1
Complicated	24	11	1
Uncomplicated	45	23	0

ulcers are present in the study, one might be led to believe that the syndrome occurs more frequently in the gastric ulcer group. The numbers here are small and therefore are probably not significant (table 6).

The incidence of postoperative hemorrhage and stomal ulcers, on the other hand, shows a ratio of 5 and 4 to 1 respectively for the two sites. One may be tempted to hazard a guess that the incidence is in some way related to the previous hypersecretion of the duodenal group and perhaps failure to resect entirely all the acid-pepsin portion of the stomach (table 6).

Anemia of the iron-deficiency type was encountered in three cases, all of whom had had previous gastric ulcers (table 6).

TABLE 6

Complications Related to Ulcer Site

	Duodenal Ulcer	Gastric Ulcer
Dumping syndrome	5	5
Hemorrhage	5	1
Stomal ulcer	4	1
Anemia	0	3
Gastrointestinal neurosis	4	0

Psychophysiologic gastrointestinal disturbances (gastrointestinal neurosis) occurred in four cases, all of whom had previously had duodenal ulcers, which would tend to support those who believe that the duodenal ulcer is a psychosomatic illness, and the gastric ulcer an entirely different entity physiologically and structurally (table 6).

Dumping Syndrome: This syndrome, as here defined, includes such features as abdominal fullness and distress some five to 30 minutes after a meal and lasting 20 minutes to two and one-half hours, frequently accompanied by nausea, vomiting of bile-stained mucus, drowsiness and lassitude,

TABLE 7

Manifestations of the Dumping Syndrome

Epigastric distress	10
Weight loss	9
Nausea	7
Vomiting	6
Flatulence	5
Weakness	5
Diarrhea	3
Nervousness	3
Sweating	3
Syncope	2
Palpitation	1
Flushing	1

and occasionally associated with cold sweats, flushing of the head and face, flatulence, palpitation or borborygmi, and rarely by syncopal attacks.

Ten patients experienced the syndrome in our study. The incidence of their symptoms is shown in table 7. It is interesting to note that nine of the 10 patients not only failed to gain weight but actually lost weight,

TABLE 8

Incidence of Dumping Following Gastrectomy

Author	Year	No. of Cases	Per Cent
Custer	1946	500	5.6
Lake	1948	615	3.0
Muir	1949	124	75.0
LaBree	1949	100	3.0
Penick	1949	90	6.6
Butler	1951	660	12.0
Meurling	1954	624	41.3
McGuire VAH	1954	74	13.5

which some authors prefer to classify as a separate postgastrectomy complication.

Examination of the past literature on the subject reveals a wide range in the incidence of dumping in the postgastrectomy patient, and there is much controversy regarding its mechanism, especially among those who believe that it is related to the surgical technic employed. Such a discussion is not within the scope of this paper (table 8).[2, 3, 5, 6, 7, 8, 9]

TABLE 9

Incidence of Stomal Ulcers Following Gastrectomy

Author	Year	No. of Cases	Per Cent
Wilkinson	1946	173	6.8
St. John	1948	373	1.4
Lake	1948	615	1.0
Penick	1949	135	0
LeBree	1949	100	1.0
McGuire VAH	1954	74	8.1

One patient in the group experienced late postprandial hypoglycemia, while three others expressed their intolerance of milk following gastrectomy.

The widely divergent figures on the incidence of dumping in table 8 may well be ascribed to a lack of uniformity in definition among various authors; consequently, we have preferred to delimit clearly our concept of its symptomatic features.

Stomal Ulcers: The reported incidence of marginal ulcers was at first somewhat variable, but as the procedure of subtotal gastrectomy became more widely employed, and more than 70% of the stomach was removed, the incidence fell sharply, so that several reports during the past five or six years claim less than a 2% incidence. Our experience has not been quite so fortunate. Five cases have been diagnosed in the 74 patients successfully followed, an incidence of 8.1%. This higher incidence is not explained, as adequate resection seems to have been carried out; but it does conform to the figure Bockus [10] believes to represent the average expectancy in the United States (table 9).[2, 3, 7, 11, 12]

TABLE 10

Incidence of Hemorrhage Following Gastrectomy

Author	Year	No. of Cases	Per Cent
Walters	1941	112	11.6
Church	1942	44	4.5
Wilkinson	1946	41	24.0
Holman	1948	53	3.8
McGuire VAH	1954	74	7.9

TABLE 11

Anemia Following Gastrectomy

Author	Year	No. of Cases	Per Cent
Rosenthal	1933	117	14.0
Watson	1947	122	12.0
Smith	1948	157	14.0
Muir	1949	124	13.7
Lyngar	1950	146	21.2
McGuire VAH	1954	74	4.0

Postoperative Hemorrhages: It has been said on several occasions that those who bleed preoperatively maintain that tendency postoperatively. This has not been our experience. Slightly less than half of our followed group had hemorrhaged grossly prior to operation. Postoperatively, of the six patients who hemorrhaged, three had hemorrhaged preoperatively and three had not, i.e., we found approximately the same tendency to bleed postoperatively in each group.

Review of the literature shows a marked variation in the tendency to

bleed postoperatively. Our study showed an incidence of 7.9% (table 10).[11, 13, 14, 15]

Anemia Following Gastrectomy: An iron deficiency anemia following gastrectomy has been reported in many instances as a postgastrectomy deficiency state and, unlike the other complications, has shown a remarkably stable incidence. Our incidence (4%) is unusually low, but represents three cases in whom levels below 12.0 gm. of hemoglobin were encountered, and no evidence of gross or occult blood in the stool was demonstrated. All three responded to oral iron therapy. Several of the cases who hemorrhaged postoperatively fell below 12.0 gm. of hemoglobin but were not included in this group for obvious reasons (table 11).[6, 16, 17, 18, 19]

Discussion

Detailed analyses of the relationships between age and race and the occurrence of postoperative complications failed to show any significant variation, nor was there any significant relationship between the over-all incidence of complications and the original site of ulceration. However, analysis of the individual complications with respect to the original ulcer site suggested that there was a greater tendency to develop the dumping syndrome and microcytic anemia in those patients who had had gastric ulcers. One patient experienced both of these complications. There also appeared to be a greater tendency for those patients who had had duodenal ulcers to develop stomal ulcers, to hemorrhage postoperatively or to manifest a gastrointestinal neurosis. No significant statistical correlation is claimed for these observations, since the numbers involved are so small. Nevertheless, it is interesting to conjecture the possible pathogenesis of these complications. It is suggested that the gastric hypersecretion of those patients with duodenal ulcers and the normal or low secretory activity of those patients with gastric ulcers may be an important factor in the production of these complications. It would appear from the experience of the past that the incidence of stomal ulceration and postoperative hemorrhage was considerably greater in those patients receiving gastroenterostomies without vagotomy or with resection of less than 70% of the stomach, presumably due to the fact that all or part of the acid and pepsin-bearing portions of the stomach remained. The introduction of vagotomy with gastroenterostomy, thus reducing the gastric secretions, and the subtotal resection removing greater than 70% of the stomach, sharply reduced the incidence of stomal ulceration with its remarkably high incidence of hemorrhage. The majority of the cases studied here received subtotal gastric resections in which attempt was made to remove approximately 80% of the stomach. It would seem possible that sufficient biologic variation exists in the extent of the acid- and pepsin-bearing portions of the stomach that in a small percentage of the cases an adequate subtotal resection, percentagewise would leave a small but significant amount of gastric mucosa, which would continue hypersecreting in

close proximity to the susceptible jejunal mucosa. As Bockus [10] has pointed out: ". . . Nothing short of total gastrectomy removes all of the acid-secreting cells in the stomach."

The relationship between personality and peptic ulcer is one frequently debated, yet it is interesting to note that all four patients with psychophysiologic disturbances in our series had previously had duodenal ulcers. Doll and Jones [20] have demonstrated that a significant relationship exists between "stressful" occupations and duodenal ulcers, whereas gastric ulcers occurred with a greater frequency among patients of poor economic means. They also pointed out the relatively low incidence among farm workers. Obviously, no significant deductions can be made from these few cases.

Three patients in this study developed hypochromic microcytic anemia as a deficiency state following gastrectomy, all of whom had had gastric ulcers prior to operation. The possibility that this state is related to the degree of acidity is raised. Since the absorption of iron is potentiated by hydrochloric acid, anemia would appear to be more likely in those patients in whom the original acid secretion was somewhat lower than normal, i.e., those with gastric ulcers, than in those who hypersecreted, i.e., those with duodenal ulcers, all other factors being equal. Needless to say, a disturbance of other factors necessary for the maintenance of normal hemoglobin levels has not been excluded.

A greater incidence of dumping in those who had had gastric ulcers was encountered, but no attempt will be made to explain this phenomenon, nor will attempts be made to discuss the surgical complications and the incidence of homologous serum jaundice.

In this study, almost half the patients successfully followed suffered one or more complications of one sort or another.

With such a high incidence of complications, it is evident that elective gastrectomy should not be lightly considered or recommended to the patient with peptic ulcer until it is apparent that the advantages from operation outweigh the risks.

Summary

1. One hundred four cases of gastrectomized peptic ulcer are reviewed. Of these, 74 cases successfully were followed up, of which postoperative complications occurred in 36.

2. Dumping syndrome occurred in 10 cases (13.5%), postoperative hemorrhages in six (7.9%), stomal ulcers in five (8.1%), gastrointestinal neuroses in four (5.4%), and anemia in three (4.0%).

3. Death at operation or very shortly thereafter occurred in three cases, a mortality ratio of 2.9%.

4. No significant relationship was shown between age at operation and postoperative complication.

5. The incidence of complication was equal in each racial group.

6. Twice as many duodenal ulcers as gastric ulcers occurred in this study, each with an equal incidence of complications.

7. Hemorrhages, stomal ulcers and gastrointestinal neuroses occurred more frequently in those patients who had had duodenal ulcers, whereas the dumping syndrome and anemia were more frequent in those who had had gastric ulcers. No statistical significance was attempted, but possible pathogenetic mechanisms are conjectured.

8. The rôle of subtotal gastrectomy in the treatment of peptic ulcer is well established, but a significant number of postoperative complications may occur which must be carefully considered before surgical intervention is recommended.

SUMMARIO IN INTERLINGUA

Ex un total de 104 patientes subjicite in le curso del passate cinque annos a subtotal gastrectomia pro benigne ulcere peptic, 74 casos esseva evalutate ab le puncto de vista del complicationes post-gastrectomial, e un essayo esseva interprendite a determinar le factores que predispone le patiente a tal complicationes.

Le complicationes incontrate esseva le syndrome del precipitate discarga gastric, ulceres del stomas, disordines de motilitate, hemorrhagias supero-gastro-intestinal, anemias a carentia de ferro, neuroses gastro-intestinal, ictero a sero homologe, morte al operation, hernias incisional, fistulas duodenal, e adhesiones intestinal con obstructiones. Un o plures de iste complicationes esseva experientiate per circa 50 pro cento del patientes includite in nostre studio.

Nulle correlation esseva evidente inter le occurrentia de complicationes post-gastrectomial e le etate o le racia del patientes.

Le numeros total del complicationes in patientes operate pro ulceres duodenal e in patientes operate pro ulceres gastric esseva equal, sed le analyse del typos individual del complicationes in relation al sito del ulcere operate pareva indicar que ulceres del stomas, grossier hemorrhagias, e neuroses gastro-intestinal esseva plus frequente in patientes operate pro ulceres duodenal durante que le syndrome del precipitate discarga gastric e del anemias a carentia de ferro occurreva plus frequentemente in patientes operate pro ulceres gastric. Nonobstante, le autores non assere que iste differentias esseva statisticamente significative. Es discutite le mechanismos possibile de alicunes de iste differentias. Illos es ponite in relation al differente nivellos de aciditate observate in le duo gruppos ante le operation.

Es presentate in grande lineas le criterios del diagnose de precipitate discarga gastric insimul con le frequentia del varie manifestationes incontrate in le presente studio.

Le frequentia del varie complicationes es comparate con datos in simile reportos publicate durante le passate dece annos. Esseva constatate un accordo general. Le autores conclude que subtotal gastrectomia, ben que le valor de iste operation es ben establite in certe casos, non es recommendabile sin caute reguardo al possibile complicationes postoperative.

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A STUDY OF NORTH AMERICAN BLASTOMYCOSIS AND ITS TREATMENT WITH STILBAMIDINE AND 2-HYDROXYSTILBAMIDINE *

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Stilbamidine and 2-hydroxystilbamidine are now widely accepted as the treatment of choice for the systemic fungus disease, North American blastomycosis. Schwarz and Goldman [1] recently reported from an epidemiologic study of blastomycosis in the United States that there were 39 cases of this disease treated with the stilbamidines during the first six months of 1953. There is a steady increase in the number of cases of blastomycosis treated with stilbamidine reported in the medical literature. These aromatic diamidines have also been used successfully in the treatment of actinomycosis [2] and sporotrichosis,[3] and have been tried (with poor results) in coccidioidomycosis,[4, 5] cryptococcosis [6] and histoplasmosis.[7, 8] Most of the articles on the use of stilbamidine and/or 2-hydroxystilbamidine in North American blastomycosis give rather enthusiastic reports of the cure of the disease. Such was the case when we first reported two cases treated by the administration of stilbamidine.[9] However, adequate follow-up studies of patients so treated have not been reported. It may be that the initial enthusiasm engendered by the report of successful results must be tempered in view of a higher relapse rate than is generally recognized. It is the primary purpose of this paper to discuss in detail our experience with stilbamidine and 2-hydroxystilbamidine, and to report the results we have obtained with these drugs in the treatment of six cases of North American blastomycosis.

The authors have had the opportunity since 1951 to study and treat six individuals with proved blastomycosis. A minimum of one year has elapsed since the last of these six patients was first started on treatment. All of these cases will be reported in great detail, since it is felt that they exhibit important features which may be of help in an understanding of the basic disease process, as well as in its treatment.

Case Reports

Case 1. Summary of Present Illness: A 38 year old Negro male automobile worker was first seen at the University Hospital on September 4, 1951, at which time he complained of painful cutaneous lesions over the back, right arm and right foot of approximately six months' duration. The patient alleged that the first sign of his

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illness was a nodule over the right wrist which occurred at the site of a cut he received from a piece of scrap steel while at work some six months previously. The nodule ulcerated spontaneously and developed into a verrucous lesion. The patient also alleged that a cut on the right foot was followed in several months by the appearance of a similar verrucous patch. Several months later a similar painful warty lesion developed over the midback.

The patient denied chills, night sweats, fever, cough or hemoptysis. He did state that he had lost some 20 pounds in weight in the two months immediately prior to his admission to the hospital. He first consulted a physician nine months after the initial disease process began and was then treated with x-ray therapy and potassium iodide orally. Improvement was very slow, and he was therefore referred to the University Hospital for a trial of stilbamidine therapy.

The patient had been born in Oklahoma but had lived in Detroit for eight years prior to his present illness.

Summary of Physical Examination: The findings on physical examination were essentially normal, with the exception of the skin. Three areas of similar involvement were found over the right medial foot, encircling the right wrist and over the midback. The largest of these areas, the one over the back, measured 15 by 20 cm. They all exhibited a verrucous appearance, with definite areas of what seemed to be spontaneous central healing. The margins of the three lesions were sharply demarcated from normal skin and were heaped up and studded with many small abscesses. Enlarged lymph nodes were present in the right axilla and inguinal regions. The heart and lungs were normal when examined by percussion and auscultation. All other findings were normal.

Summary of Laboratory Findings: The admission blood work showed a hemoglobin of 14.0 gm. %, with a red blood count of 4.2 million/cu. mm. The white blood count was 6,300/cu. mm., with a differential count of polys, 83%, lymphocytes, 24%, eosinophils, 1%, and monocytes, 2%. The admission urinalysis showed a 4 plus sugar reaction. Fasting blood sugar was 216 mg. %. The budding forms of *Blastomyces dermatitidis* were found easily on microscopic examination of pus expressed from all three of the cutaneous lesions. Microscopic examinations were also made of the small amounts of sputum the patient raised. These were also positive for *B. dermatitidis.* Cultures of both sputum and cutaneous pus were positive for the fungus. Repeated examinations and cultures for acid-fast organisms were negative. The old tuberculin skin test was positive at 1:1,000 dilution in 48 hours. The initial blastomycin skin test was negative in 1:100 dilution. One month after admission, however, a strongly positive blastomycin skin test in 1:1,000 dilution was obtained. Complement-fixation studies on the serum were not done. Biopsy of the cutaneous lesions failed to reveal organisms. The pathologic findings, however, were typical of the type of granulomatous reaction found in North American blastomycosis.

Summary of X-rays: Frontal stereoscopic and lateral x-ray films of the chest revealed a patchy area of increased density localized to the right upper lobe. This was felt to represent active disease. Survey of the bones failed to show any osseous defects.

Summary of Course: After the diagnosis of North American blastomycosis was established, and after the patient's apparent diabetes mellitus was controlled, therapy with stilbamidine was begun. This was given by intravenous drip method in a dosage of 150 mg. per day for 12 days. The drug was tolerated well and no signs of toxicity occurred. Partial healing took place. However, organisms could still be obtained from both sputum and cutaneous pus. Accordingly, further stilbamidine was started one month following the administration of the first course. Eight doses of 150 mg. each were given intravenously. The drug was stopped at this time because of the gradual development of a leukopenia of 3,600/cu. mm. The patient therefore received a total of 3.0 gm. of stilbamidine. Continued improvement ensued, and on December

5, 1951, he was discharged as an apparent cure. He did not show any evidence of stilbamidine neuropathy. He was re-admitted for three days of study on January 28, 1952, and was found to be free of evidence of active disease. No blastomycetes could be found on scrapings of the completely healed cutaneous lesions or from the sputum. The x-ray appearance of the lungs showed slight change, which was interpreted as beginning fibrosis. The patient has remained well and was last heard from on September 1, 1954, at which time he was working steadily, had had no further treatment and felt well.

Case 2. Summary of Present Illness: A 41 year old Negro male was first seen at the University of Michigan Hospital on May 21, 1948, at which time he complained of weight loss and cough of six weeks' duration. He dated the onset of his illness to Easter day, 1948, when he had had a sudden onset of a severe chill, followed by a fever of 102° F. His fever had persisted in an intermittent manner and subsequently was accompanied by a gradual loss of weight, night sweats and a cough productive of greenish, blood-streaked sputum. A specimen of this sputum was reported by the Michigan Department of Health Laboratory as being culturally positive for *Blastomyces dermatitidis.* The patient was then referred to the University Hospital for treatment.

Summary of Physical Examination: At the time of hospitalization this patient appeared to be chronically ill. His temperature was 100° F.; pulse, 80/minute; respirations, 30/minute; blood pressure, 120/75 mm. of Hg. His weight was 113½ pounds. (Alleged previous average weight was 140 pounds.) There was no abnormality of the skin other than an obvious generalized ichthyosis. There was percussion dullness over the right lower posterior lung field, as well as decreased breath sounds and increased tactile and vocal fremitus in this area. The heart was normal when examined except for the presence of a soft systolic murmur, heard best to the left of the sternum in the right fourth intercostal space. There were enlarged, nontender axillary lymph nodes present bilaterally. The remainder of the physical examination revealed essentially normal findings.

Summary of Laboratory Findings: The admission hemoglobin was 10.0 gm. %, with a red blood count of 3,270,000/cu. mm. The white blood count was 10,000/cu. mm., with a differential count of polys, 81%, lymphocytes, 14%, monocytes, 5%. The urinalysis was entirely normal. The Kahn reaction was negative. A potassium hydroxide preparation of the sputum revealed numerous single budding fungi consistent in appearance with *B. dermatitidis.* This fungus was cultured from the sputum. *B. dermatitidis* was subsequently cultured on many occasions from cutaneous lesions, draining sinus tracts and urine. A blastomycin skin test was not done at the time of the initial hospitalization, nor were complement fixation studies done in 1948. Repeated blastomycin skin tests done on later visits had always been negative, while complement-fixation antibody titers of 1:128 and 1:256 were reported on September 11, 1953, and June 28, 1954, respectively. Biopsies have been taken on many occasions from the cutaneous lesions which developed during the course of his illness. All of these showed the typical granulomatous response evoked by *B. dermatitidis,* and several of the specimens revealed the organisms of *B. dermatitidis* in tissue. Serum protein studies showed a total protein of 7.7 gm. %; albumin, 3.3%; globulin, 4.4%, with an A/G ratio of 0.8. This reversal of the albumin-globulin ratio was constant on all hospital admissions.

Summary of X-rays: Chest films revealed very extensive zones of abnormal increased density occupying all of the right lower lobe except for the apical segment and the left midlung field. There was moderate elevation of the dome of the right diaphragm. X-ray films on subsequent hospitalizations showed extensive destructive bony changes in the ribs, vertebrae, right tibia and lower end of the left humerus.

Summary of Course: At the time of this report this patient has had nine separate admissions to the University Hospital and innumerable visits to the Dermatology

Out-Patient Department. When he was first admitted the disease process appeared limited to the lungs. Cutaneous lesions and subcutaneous abscesses developed while he was in the hospital and have since appeared on many occasions over the face, trunk and extremities. Extensive bony involvement has occurred, and at one time the orthopedic surgeons felt that amputation of the left arm was advisable. Prior to the institution of stilbamidine therapy in August, 1951, the patient had been treated by oral potassium iodide in amounts which reached 16 c.c. of the saturated solution three times per day; Acti-dione, 40 mg./day intramuscularly for 12 days; deep x-ray therapy to the lungs; sulfadiazine, 6.0 gm. per day for nine months; an experimental fungicide, XG, given intramuscularly, intravenously and by inhalation routes; cortisone, 1.8 gm. in two weeks' time; massive amounts of penicillin and Chloromycetin, and dihydroacetic acid. In spite of this impressive array of medicaments the patient's disease process became gradually more extensive. He developed blastomycotic prostatic involvement which necessitated a prostatic resection.

He was placed on the University Hospital "danger list" and death was imminent at the time stilbamidine was first administered, in August, 1951. His over-all course since that date has been characterized by gradual improvement in the disease process, with healing of the bone lesions and cutaneous lesions, and x-ray evidence of improvement of the extensive pulmonary lesions. Nevertheless, many new blastomycotic subcutaneous abscesses and skin lesions developed up until the time of the last hospitalization, on May 24, 1954. He has been free of evidence of activity of the disease process since his discharge on June 28, 1954, although experience tempers one's hopeful expectations that a cure has been obtained. He has received stilbamidine in the following amounts:

8-11-51 to 8-17-51	0.60 gm. stilbamidine isethionate
9-12-51 to 9-21-51	1.80 gm. stilbamidine isethionate
10-13-51 to 10-23-51	1.50 gm. stilbamidine isethionate
1-4-52 to 2-24-52	3.30 gm. stilbamidine isethionate
3-29-52 to 4-14-52	2.25 mg. stilbamidine isethionate
7-19-52 to 8-13-52	3.90 gm. stilbamidine isethionate
3-5-53 to 3-25-53	3.15 gm. stilbamidine isethionate
5-31-54 to 6-23-54	6.00 gm. stilbamidine isethionate
Total	22.50 gm stilbamidine isethionate
8-28-53 to 9-29-53	2.80 gm. of 2-hydroxystilbamidine isethionate
Combined Total	25.30 gm.

The stilbamidine was all given in doses of 100 to 150 mg., dissolved in intravenous fluid. Courses of therapy of 12 to 21 days each were usually given. During the last hospitalization, in May, 1954, the stilbamidine was given in doses of 150 mg. per day for 16 consecutive days, followed immediately by 12 days of 300 mg./day. At no time during the three and one-half years since stilbamidine was first administered has there been any sign of fifth nerve involvement. The white blood count dropped to levels below 3,000 cells/cu. mm. on two occasions during this therapy. The leukocyte count, however, always returned to normal values within two weeks following cessation of therapy. No signs of toxicity other than this and nausea have developed. The 2-hydroxystilbamidine therapy was discontinued on September 29, 1953, because of the development of abnormal liver function studies. These also reverted to normal soon after the drug was stopped.

Case 3. Summary of Present Illness: A 34 year old white housewife was first seen at the University Hospital on June 9, 1952, at which time her chief complaint was that she had been coughing up blood-streaked sputum for the previous five months. The patient related that she had been quite well until she developed what she thought was a severe chest cold and began to raise small amounts of blood-streaked sputum. She did not recall experiencing chills, night sweats or fever at

that time. The productive cough continued and increased slightly in severity, but she did not seek medical care until she developed severe, sharp, stabbing pain in the right upper quadrant of the abdomen. This pain was most severe on deep inspiration, did not radiate and was transitory in nature up until the time of admission to the University Hospital. At the time the upper abdominal pain occurred the local physician was consulted. He was unable to demonstrate any abnormality of the lungs by x-ray examination, and therefore sent sputum specimens to the Menominee, Michigan Laboratory for examination and culture. One of these specimens was reported as being positive for the presence of *B. dermatitidis* by culture. Treatment with potassium iodide was then begun, but was discontinued in six days because of the appearance of erythematous nodular lesions over the right knee and left lower leg. Several days later the patient also noticed tender swelling over the left anterior shin, right foot and both hands. She was then referred to the University of Michigan Hospital for treatment.

The patient had lived in cities in northern Michigan and Wisconsin during her lifetime. She had enjoyed good health, without previous serious illness. The remainder of the history was noncontributory to the present illness.

Summary of Physical Examination: The patient was an afebrile, well nourished white female in no apparent distress. She was alert and coöperative. There was a discrete, erythematous, slightly tender firm nodule over the left inner thigh, the left lower leg and the right outer thigh. A granulomatous, crusted lesion with a peripheral circlet of pustules, 1.25 inches in diameter, was found over the anterior right knee. On the left shin and dorsum of the right foot diffuse, hard, slightly tender, firm swellings were noted. These seemed to be attached to the deeper underlying tissue and resembled erythema nodosum. Examination of the lungs revealed no definite abnormalities by percussion and auscultation, except for a few crepitant inspiratory râles heard over the right base. The heart was normal in size by percussion. The rate was 68 per minute. The rhythm was regular and no murmurs were heard. The blood pressure was 138/78 mm. of Hg. The abdomen was normal by examination. No lymphadenopathy was found.

Summary of Laboratory Studies: The admission hemoglobin was 13.5 gm. %; red blood count, 5.0 million/cu. mm.; hematocrit, 48.0; MCV, 96; sedimentation rate, 37 mm./hr., corrected (Westergren method). The white blood count was 14,800/cu. mm., with a differential count of polys, 77%, lymphocytes, 12%, monocytes, 5%, eosinophils, 3%, basophils, 2%. The urine examination was normal except for a trace of albumin on one occasion. Direct microscopic examinations of 15% potassium hydroxide preparations of sputum and pus from the lesion of the right knee were positive for the single budding forms of *B. dermatitidis*. Room temperature and 37° C. cultures of sputum and pus were also positive for *B. dermatitidis*. The blastomycin and old tuberculin skin tests were negative at 24 and 48 hours. Blastomycin complement fixation studies were positive in a dilution of 1:32. Biopsies were taken of the granulomatous knee lesion and also from one of the tender nodules of the left shin. The findings from the latter nodule were pathologically consistent with the diagnosis of erythema nodosum, while the histopathologic changes found in the knee lesion were those of a chronic suppurative granuloma. No fungi were found by examination of the slides of either lesion by the routine hematoxylin and eosin stain, or the periodic acid-Schiff stain.

Summary of X-Rays and Consultation: Stereoscopic antero-posterior films of the chest showed a normal mediastinal and cardiac silhouette. There was a calcified parenchymal scar in the left hilum, together with bilateral apical pleural thickening. There was, therefore, no definite evidence of active pulmonary disease. A complete bone survey was negative for evidence of disease process. Because of the relatively negative x-ray findings of the chest, the patient was seen in consultation by a member

of the Thoracic Surgery Department; bronchoscopy was performed and was reported as showing a completely normal tracheobronchial tree. No evidence of a bleeding site to account for hemoptysis was seen.

Summary of Course: At the time of admission to the University Hospital on June 9, 1952, the patient was raising approximately one-half cupful of blood-streaked sputum each day, and the cutaneous lesions appeared to be increasing in size. Accordingly, after the fungi were found by direct examination, treatment with stilbamidine was begun. This was given in consecutive doses of 150 mg. per dose. The drug was dissolved in 500 c.c. of 5% glucose in distilled water and was given by slow intravenous drip daily for a total of 22 days (total stilbamidine dosage, 3.3 gm.). During the time the drug was being given the patient exhibited no untoward reactions other than mild chills on two occasions and increasing impairment of the sensory component of the fifth cranial nerve. The cutaneous lesions healed and the hemoptysis ceased during the administration of the drug. No organisms could be found at the time of her discharge from the hospital on July 9, 1952. The patient then returned to her home in the upper peninsula of Michigan and subsequently moved to northern Wisconsin. She has not been seen in follow-up visits. Detailed reports, however, have been obtained from both the patient and her physicians. Four and a half months after her discharge from the hospital the lesion over the right knee became ulcerated and has continued to drain pus. The size of the lesion has increased, according to the patient. *B. dermatitidis* has been recovered many times.

It is not known at the time of this report whether this patient has sought further medical care for her active disease.

Case 4. Summary of Present Illness: A 35 year old white housewife was first seen at the University Hospital on October 6, 1952, at which time her major complaint was of an unsightly cutaneous lesion of the nose. She dated her illness to November, 1950, when she noted the insidious onset of shortness of breath, followed by a small hemoptysis. She consulted her local physician and, at his suggestion, an x-ray film of the chest was taken. This film was reported as showing an abnormality of some type. However, no further investigation or treatment was carried out until some one and a half years later, when verrucous granulomas appeared on the nose, the right neck, the forearm, thigh and scalp. The patient was then referred to a dermatologist, who established the diagnosis of North American blastomycosis by finding the fungi in pus from the cutaneous lesions and from the sputum which the patient continued to raise. Treatment was instituted which included a course of superficial x-rays, saturated solution of potassium iodide and diethylstilbestrol. Gradual objective improvement of all skin lesions, except that involving the nose, occurred during the ensuing six months. The sputum continued to be blood-streaked, and the patient was therefore referred to the University Hospital for further treatment. The remainder of the history was noncontributory. The patient had been a life-long resident of a small Illinois town. She was married and had one healthy child.

Summary of Physical Examination: Upon examination this patient appeared to be in good health. She was afebrile and, except for the cutaneous system, did not exhibit any abnormal physical finding. There were healed atrophic scars over the right thigh, right forearm and right posterior neck. A verrucous, slightly erythematous lesion was present over the tip of the nose. Pus could be expressed from the many sites throughout this lesion when slight pressure was exerted. Careful examination of the heart and lungs failed to reveal any deviation from normal. The abdomen was normal, and no significant lymphadenopathy was present.

Summary of Laboratory Findings: The admission hemoglobin was 12.5 gm. %, or 80% of normal. The red blood count was 4.7 millions per cubic millimeter; hematocrit, 41.0; sedimentation rate, 37 mm. per hour, corrected (Wintrobe method). The white blood count ranged from 7,800 to 9,200 per cubic millimeter, with a differen-

tial count of polys, 61%, lymphocytes, 26%, monocytes, 10%, eosinophils, 2%, and basophils, 1%. The urinalysis was completely normal.

The single budding organisms of *B. dermatitidis* were readily identifiable upon potassium hydroxide examination of the sputum and of pus taken from the cutaneous lesion of the nose. The pathogen was also successfully cultured on Sabouraud's glucose agar from both sputum and cutaneous pus. The blastomycin skin test was negative at 24 and 48 hours in a dilution of 1:1,000 at the time of admission. This was not repeated at a later date, nor were studies done for the presence of complement-fixing antibodies. A biopsy was taken from the cutaneous lesion of the nose, but sufficient healing had already taken place to prevent the finding of the typical granulomatous appearance of cutaneous blastomycosis. Instead, the changes reported were those of a connective tissue hyaline scar. No ulcerated areas were found.

Summary of Course: At the time this patient was admitted to the University Hospital her disease process appeared to be at a standstill. There was no question but that she had experienced decided benefit from the treatment administered prior to her hospitalization, yet this means of therapy did not appear adequate to eradicate the entire disease. On October 9, 1952, she was accordingly started on intravenous stilbamidine, given in daily doses of 150 mg. in 500 to 1,000 c.c. of sodium chloride solution. This was given for 20 consecutive days for a total dosage of 3.0 gm. of stilbamidine. Improvement of the nose lesion was apparent within the first week after stilbamidine was instituted. Within a 20 day period complete healing was apparent. No signs of stilbamidine toxicity were exhibited during the administration of the drug. However, some two months after discharge from the hospital she noted the gradual onset of sensory impairment over the distribution of the fifth cranial nerve. This has continued to date, without showing improvement. Follow-up studies have been done on this patient and she has remained well and free of objective or subjective symptoms which might be interpreted as due to *B. dermatitidis* infection to the present time. The changes described on the original x-rays have persisted to date. No cough, sputum or hemoptysis is present.

Case 5. Summary of History: A 37 year old white male factory worker was first seen at the University Hospital on February 11, 1945, when he complained of having "sores" over the neck, left arm and left foot of nine months' duration. These areas increased gradually in size, and very soon afterwards he noted similar lesions over the left arm and foot. No treatment was sought until an examination and x-rays of the chest were done prior to his entry into the U. S. Armed Forces. He was then told that he had pulmonary tuberculosis and was sent to a sanatorium. Biopsies and smears of the cutaneous lesions were then done and were reported as showing blastomycetes. He was accordingly transferred to the University of Michigan Hospital for evaluation.

At the time of admission to the hospital he gave the history that some three months prior to the known onset of his illness he had cleaned out a dusty cellar. Following this, he had had "pleurisy," which cleared up spontaneously. He denied fever, weight loss, chills or night sweats. He had been a foundry worker in Michigan for the three years prior to the development of his illness. The remainder of the history was not contributory to his illness.

Physical Examination: At the time of admission the patient appeared to be in good health. His temperature, pulse, respiratory rate and blood pressure were normal. Three cutaneous lesions were present on the skin. The largest area of involvement extended over the entire right neck region. A 5 by 8 cm. lesion was present over the left posterior upper arm, and a 3 by 3 cm. circular area of involvement was found over the inner aspect of the arch of the left foot. These areas all exhibited sharply defined, heaped-up verrucous borders which were studded with small abscesses. The lungs were clear to percussion and auscultation. Physical examination yielded no other pertinent findings.

Summary of Laboratory Findings: The admission hemoglobin was 16.8 gm. %; red blood count, 6.0 million per cubic millimeter. White blood count was 10,450 per cubic millimeter, with a differential count of polys, 60%, lymphocytes, 34%, eosinophils, 4%, monocytes, 2%. Urinalysis was normal. The blood Kahn reaction was negative. *B. dermatitidis* was seen on direct microscopic examination of both cutaneous pus and sputum, and was also obtained in pure cultures from both sources. Biopsies of the cutaneous lesions revealed many single-budding, doubly-contoured blastomycetes. Unfortunately, neither complement fixation nor skin testing was done at the time of the admission in 1945. When the patient was re-admitted, in 1953, the blastomycin skin test was negative in dilutions of 1:1,000, 1:100 and 1:10. The complement-fixation titer was 1:10. Subsequent blastomycin skin tests have been negative, while the complement-fixation titers had risen to 1:40 when last done (December 13, 1954).

Summary of X-rays: The initial films of the chest, done on February 13, 1945, showed infiltration with cavitation of the right apex. Complete bone survey was normal. No films were taken from 1945 until re-admission in 1953. Chest films taken on January 7, 1953, then revealed an extension of the pulmonary lesion of the right upper lung, with questionable new lesions in the left upper and right lower lung. These lesions have persisted until the time of this report, with the exception that the right apical cavity cannot be visualized on the more recent films. Skeletal survey has continued to be negative.

Summary of Course: The hospitalization in 1945 was for 16 days only. No sign of improvement was apparent at the time of the patient's discharge, and he went home on potassium iodide therapy. He took potassium iodide almost continuously from 1945 until he returned to the University Hospital in January, 1953. During this time he had also received eight treatments of superficial x-ray from various physicians.

In 1952 he developed new facial lesions, one of which destroyed a large portion of the right lower eyelid. The foot lesion had healed completely, although all other areas of cutaneous involvement were gradually enlarging. He was also raising small amounts of greenish sputum. No blood had been noted in the sputum. His first course of stilbamidine was begun on January 2, 1953, and consisted of daily intravenous injections of 150 mg. of stilbamidine isethionate, given in from 300 to 500 c.c. of saline for a total of 35 doses. The response to this first course of therapy was dramatic. The cutaneous lesions appeared to be completely healed. However, the x-ray of the chest still revealed extensive disease, and blastomycetes could be recovered from the sputum. Breakdown of the cutaneous lesions occurred within two months after the stilbamidine was stopped.

His complete stilbamidine treatment to date is best summarized:

1-2-53	2-7-53	5.25 gm.	Stilbamidine isethionate
3-10-53	3-31-53	2.25 gm.	Stilbamidine isethionate
5-26-54	7-8-54	3.00 gm.	Stilbamidine isethionate
8-10-54	8-27-54	5.10 gm.	Stilbamidine isethionate
		15.60 gm.	

The last course of stilbamidine was given from August 10 to August 27, 1954, and was administered in a dosage of 300 mg. each day for 17 consecutive days. During this course the patient at first appeared again to make a rapid recovery, whereas the drug given earlier in 1954, in the conventional dosage of 150 mg./day, seemed to have very little effect on the progress of the disease. Nevertheless, it was felt that complete clearance of the disease process could not be obtained from stilbamidine alone when a total of 5.1 gm. of the drug had been given during the short period of 17 days. Impairment of the sensory portion of the fifth cranial nerve had occurred in 1954, after the third course of stilbamidine. This finding has remained persistent. At the time of this report this patient is being treated with one of the nitrostyrene

derivatives. A report of this type of therapy will be published separately. At the time these newer drugs were begun, extensive cutaneous and pulmonary involvement existed and the disease process appeared to be gradually progressing.

Case 6. (Courtesy of U. S. Veterans Administration Hospital, Ann Arbor, Michigan.) *Summary of Present Illness:* A 47 year old white male first entered the U. S. Veterans Administration Hospital at Dearborn, Michigan, on September 26, 1953, with the major complaint of enlarging "cancers" of the right cheek (figure 1) and the left lower gum (figure 2) of three months' duration. He stated that in May, 1953, he had noted a small white ulcerating lesion of the gum line on the left side of the lower jaw. The lesion gradually increased in size and was said to be due to poorly fitting dentures. Then during the first week in June, 1953, a small nodule appeared over the right malar prominence and increased rapidly in size. The patient was receiving penicillin injections from his local physician during this time. A biopsy of the cheek lesion was performed when no response to antibiotics was obtained.

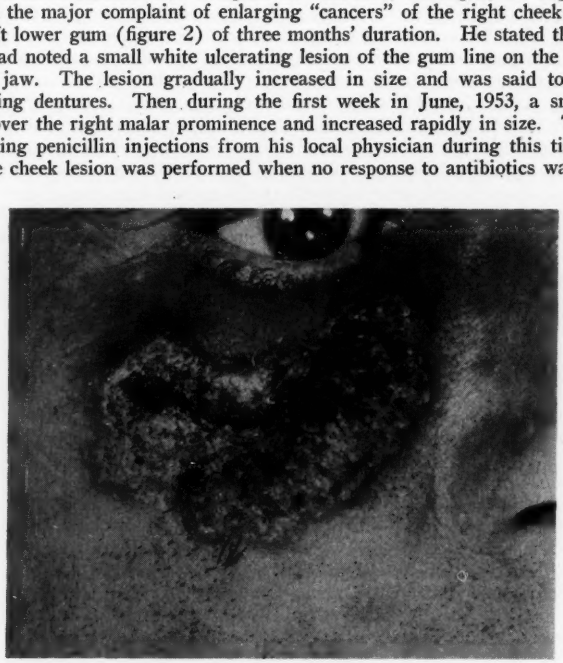

FIG. 1. Cutaneous lesion of right cheek prior to initial 2-hydroxystilbamidine therapy (case 6).

The pathologic report was that of a Grade I squamous cell carcinoma. He was then referred to the U. S. Veterans Administration Hospital, Dearborn, Michigan, for treatment of the cutaneous neoplasm.

The patient denied chills, fever, night sweats or cough. He had lost 10 pounds in weight in the three months prior to hospitalization. He had been born in Kentucky but had lived in Detroit for many years, where he worked as a cushion builder for the Chrysler Corporation. He gave a history of primary syphilis in 1929, treated at the U. S. Veterans Administration Hospital in Dayton, Ohio.

Summary of Physical Examination: On physical examination the patient was found to be well nourished and well developed. He did not appear ill. The pulse rate was 108/minute; blood pressure, 130/70 mm. of Hg; temperature, 98.6° F; weight, 175 pounds. Examination of the skin showed a 1.5 by 3 cm. ulcerating lesion under the right eye. This was verrucous in appearance and had a sharp margin which was heaped up and studded with many small abscesses. In the mouth there was a 0.5 by 1 cm. white ulcerated lesion on the gum line on the left side of the

mandible, and a nodular, plaque-like lesion, 2.5 cm. in diameter, beneath the left side of the anterior tongue. The patient was edentulous. Examination of the lungs was normal by percussion and auscultation. The heart was normal in size. The rhythm was regular, and no murmurs were heard. The remainder of the physical examination was essentially negative.

Summary of Laboratory Findings: The admission hemoglobin was 15.5 gm. %. White blood count was 10,800/cu. mm., with a differential count of polys, 68%, lymphocytes, 28%, monocytes, 2%, and eosinophils, 2%. The urinalysis was normal. The blood Kahn test was doubtful. Liver function studies were entirely normal, as were the kidney function studies. The direct potassium hydroxide microscopic examinations of pus obtained from the edge of the cutaneous facial lesion and from the ulcerating mouth lesion were positive for the single budding organisms of *B. dermatitidis*. Cultures of this fungus were also obtained on many occasions when pus from

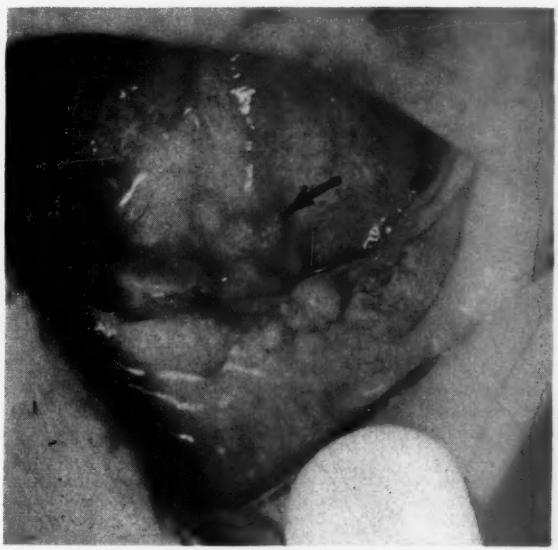

FIG. 2. Blastomycotic lesions of the floor of the mouth (case 6).

the oral and cutaneous lesions was inoculated on Sabouraud's and blood agar. A culture positive for *B. dermatitidis* was also obtained on one occasion from a specimen of gastric washing. Biopsies of the oral and cutaneous lesions revealed pseudoepitheliomatous hyperplasia and a granulomatous infiltrate in the dermis. Numerous organisms were found on both biopsy specimens. The blastomycin skin tests in dilutions of 1:1,000, 1:100 and 1:10 were negative throughout the course of his disease. Complement fixation studies were not done at the time of his initial hospitalization; however, they were positive in a dilution of 1:5 on October 12, 1954. Bone marrow examination was normal.

Summary of X-ray: X-ray studies of the chest failed to reveal any abnormalities. Repeated films of the bony system, including the mandible and facial bones, also failed to exhibit any defects.

Summary of Course: Soon after the correct diagnosis of North American blasto-

mycosis was established by finding the fungi in potassium hydroxide preparations, the patient was started on a course of 2-hydroxystilbamidine. This was administered in a dosage of 225 mg. per day, given by the intravenous drip method. This method of administering the drug was used through his long hospitalizations. The patient responded in a very favorable manner to the first course of 2-hydroxystilbamidine, which was started on October 21, 1953. By the time the 20-day course of therapy was completed the cutaneous and oral lesions had shown almost complete healing. Three weeks afterward, however, new small pustules were noted along the lower left gum margin. Accordingly, another course of 10 injections of 2-hydroxystilbamidine was given. No untoward symptoms developed, and complete healing was apparent. The patient returned to work, only to experience recurrence of the granulomatous and pustular areas at the site of the left lower gum. Smears, cultures and a biopsy were positive for the presence of *B. dermatitidis,* and a third course of the 2-hydroxy derivative of stilbamidine was given over a 20-day period. Again, apparent complete healing occurred, and at the time of the patient's discharge from the hospital, February 23, 1954, he was started on a saturated solution of potassium iodide, 6 gm. three times a day. He remained apparently well until approximately June 1, 1954, when he noticed a diffuse swelling and soreness of the entire lower lip. He received innumerable injections of penicillin for this from his local physician prior to his rehospitalization on July 1, 1954. Scrapings and cultures of the many small abscesses present over the inner surface of the lower lip all revealed *B. dermatitidis.* Again, 2-hydroxystilbamidine was given, this time for 21 consecutive days. Again, temporary improvement occurred for one month's time, during which the patient felt well and remained active.

Treatment was resumed on September 18, 1954, when new pustules developed on the inner lip. This was given for 10 days, at which time the patient was transferred to the U. S. Veterans Administration Hospital in Ann Arbor, Michigan. He was then started on stilbamidine, in doses of 300 mg. each, given daily by intravenous drip. A rapid decrease in the size of the lower lip occurred while on this drug. However, treatment had to be discontinued because of uncontrollable nausea and vomiting. No other signs of stilbamidine toxicity occurred. The patient was last seen on January 10, 1955, at which time large granulomas were present for the first time on the outer surface of the lower lip. The patient refused hospitalization at this time.

Below is a summary of stilbamidine and 2-hydroxystilbamidine to date:

10-21-53	11-9-53	4.5 gm.	2 hydroxystilbamidine isethionate
12-9-53	12-19-53	2.25 gm.	2 hydroxystilbamidine isethionate
1-8-54	1-28-54	4.5 gm.	2 hydroxystilbamidine isethionate
7-1-54	8-22-54	4.725 gm.	2 hydroxystilbamidine isethionate
9-18-54	9-28-54	2.25 gm.	2 hydroxystilbamidine isethionate
		18.225 gm.	2 hydroxystilbamidine isethionate
10-12-54	10-21-54	2.7 gm.	Stilbamidine isethionate
Combined total		20.925 gm.	

Clinical Considerations

It is felt that all six of these patients represent examples of systemic North American blastomycosis. This statement is made in spite of the fact that cases 3 and 6 have not exhibited any positive clinical evidence of systemic disease. A study of case 3 is of particular interest, since the fungi were seen and cultured from the blood streaked sputum, yet no demonstrable pulmonary focus of infection could be found to account for this sputum, even though extensive x-ray studies were done and bronchoscopy was performed.

Undoubtedly, had our attention not been drawn to the pulmonary system by the bloody sputum, we would have overlooked this focus of involvement. Case 6 has not shown demonstrable blastomycotic disease of any system other than the skin and mucous membranes, yet it does not seem plausible that multiple sites of primary inoculation have occurred. We would prefer to agree with the concept of the primary inoculation type of North American blastomycosis first advocated by Schwarz and Baum,[10] and recently elaborated upon by Wilson et al.[11] These authors feel that the only true type of primary cutaneous inoculation blastomycosis is typified by the occurrence of a primary "chancre-like" lesion with satellite lymphadenopathy. It is probable that this type of disease is very rare. Complete recovery had been the rule in the few authentic case reports of this primary inoculation disease.

Case 1 is of interest in this respect, for even though a demonstrable pulmonary focus existed, and blastomycetes were seen and cultured from the sputum, the patient was diagnosed originally at the University Hospital as having cutaneous and pulmonary blastomycosis. The patient alleged that an industrial accident preceded the appearance of the ankle and arm lesions and, on the strength of this, was awarded compensation by the courts, since it was felt that the disease had been acquired by inoculation at the time of these accidents. In retrospect, there is little doubt that the pulmonary focus served as the site of origin, and that the cutaneous lesions simply represented dissemination from this focus. Cases 2, 4 and 5 have all had demonstrable systemic disease involving the lungs and skin; case 2 also had extensive bony, subcutaneous and prostatic disease.

Case 6 is a rarity among proved cases of North American blastomycosis in that true mucous membrane involvement was present and has been the prominent focus of recurrence. Absence of mucous membrane and gastrointestinal involvement has been one of the clinical points often stressed in mycology textbooks as differentiating this disease from the South American type of blastomycosis and also from histoplasmosis. This man has also not shown pulmonary involvement, yet the authors feel it is unlikely that primary inoculations occurred in the mouth and right cheek within a month's time. Rather, it would seem plausible that the organisms were being disseminated to those areas from some central focus, possibly an undiscovered pulmonary focus.

Cases 2 and 5 are also of interest from the standpoint of the length of time their disease process had existed. Case 2 has been followed closely for a total of seven years, while case 5 has had North American blastomycosis for a full 10 years, in spite of the use of large amounts of stilbamidine. Of the six patients covered in this report, all are alive at the time of this writing. Two of the six (cases 1 and 4) are completely free of the disease and have remained so for at least two years. Case 2 was apparently well at the time of discharge from the hospital in October, 1954. One glance at his hospital record of nine admissions causes one to doubt that a

permanent cure has been effected. Three patients (cases 3, 5 and 6) still have active disease and need further treatment.

Immunologic Aspects and Stilbamidine Therapy

It is not possible to evaluate properly the immunologic status of all of these six patients, since adequate skin testing and complement-fixation tests were not performed in all instances. Nevertheless, from the findings obtained there appears to be some correlation between the outcome of the disease to date and the immunologic response elicited. Smith [12] has grouped the existing immunologic types of blastomycosis and found that the best prognosis can be expected from those individuals showing positive blastomycin skin tests and negative complement-fixation studies. The converse is also true, in that negative blastomycin skin tests and positive complement-fixation titers indicate a poor prognosis. Similar interpretation of the skin testing and complement-fixation studies has been given by workers in the other deep fungus diseases, histoplasmosis and coccidioidomycosis.

Only one of this group of six patients (case 1) exhibited a positive blastomycin skin test. This patient did not have complement-fixation studies done. It is probable, though, that complement-fixation antibodies were not present, since this individual responded well to small amounts of stilbamidine (3.0 gm.) and has remained free of evidence of active disease. The clinical course of case 4 is somewhat contradictory to the calculated prognostic outcome in that this patient's skin test was negative. Complement-fixation studies were not reported. Yet this patient also showed a rapid response to the administration of 3.0 gm. of stilbamidine and has remained free of the disease for two years. It is unfortunate that repeat skin tests were not done at the time this patient returned for follow-up visits. It might logically be expected that she would show a positive skin test at this time.

Cases 2, 3, 5 and 6 have all shown negative skin tests. All four of these cases have also exhibited repeated relapses following stilbamidine therapy, and at least three still have active disease. Complement-fixation studies were not done on case 3; however, the other three patients have exhibited significant complement-fixation titers. The three patients who present this picture of a negative skin test and positive complement-fixation test have had a combined total of 61.825 gm. of stilbamidine isethionate or 2-hydroxystilbamidine, yet in spite of this therapy, the disease persists. These findings give reason for speculation that perhaps it is the natural immunologic response to the disease process, more than anything else, that governs the favorable or unfavorable results of the present-day stilbamidine treatment. There is also some reason to suspect that the present accepted dosage schedule of stilbamidine and 2-hydroxystilbamidine is in need of reëvaluation.

The most frequently used dose of stilbamidine is 150 mg. per day, while 2-hydroxystilbamidine is given in doses of 225 mg. per day. These

amounts were used in the treatment of all six patients covered in this report, with the exception of the most recent treatments given to cases 2, 5 and 6. In each of these three patients, stilbamidine was given in amounts of 300 mg. per day instead of 150 mg. In fact, case 2 was given a total of 6.0 gm. in a 24 day period. This brought the total amount of stilbamidine given this patient to a total of 22.5 gm. The response to this increased amount of the drug certainly seemed to be more favorable, and at the time of this writing there has been no recurrence of the disease process. Cases 5 and 6 also showed a more favorable and rapid clinical response to 300 mg. of stilbamidine each day than they had on previous occasions, when treated with the conventional dosage schedule. Amounts of stilbamidine in doses of 300 mg. per day appeared to be as well tolerated as the smaller dosage by these three patients. Case 6 did develop extreme nausea and vomiting while under treatment. It should be recorded, though, that the same nausea had occurred while he was being treated in amounts of 150 mg. per day. Toxicity to stilbamidine appeared in four of these six patients. The total amount of the drug given each patient did not apparently play the deciding rôle in the production of the sensory changes of the trigeminal nerve. Case 2 has received the greatest total amount of stilbamidine (22.5 gm.), and as yet has shown no signs of toxicity other than a transient leukopenia. In contrast, in case 4, who was given a total of only 3.0 gm. of stilbamidine, rather severe fifth nerve sensory changes appeared and have persisted in a modified form to the time of the last check-up. The sensory impairment experienced in case 3 has been quite profound and has extended to include the entire upper extremities. This developed within two months of the time the first course of 3.3 gm. of stilbamidine was given. As stated previously, there seems to be no correlation between dosage of the drug given and sensory nerve impairment. It is of interest, though, that cases 1 and 2, neither of whom developed neurologic change, are both Negroes, while the remainder of the cases were of the white race.

Summary

Six cases of proved North American blastomycosis are reported in detail. All six patients are felt to represent systemic blastomycosis acquired by means of inhalation of *B. dermatitidis* rather than by percutaneous inoculation. All six patients have been treated with varying amounts of stilbamidine or 2-hydroxystilbamidine. Four of these six patients have had repeated recurrences of active blastomycosis in spite of the administration of stilbamidine and 2-hydroxystilbamidine. One of these four patients has had active disease for a total of 10 years, while a second patient with blastomycosis has been under observation for seven years. The blastomycin skin tests were negative in five of the six cases, including the four individuals in whom relapses have occurred. Significant complement-fixation titers were also obtained in three of the cases who have relapsed after what was con-

sidered adequate amounts of stilbamidine. It is suggested that the immunologic status may play a very significant rôle in the cure of this disease with stilbamidine and/or 2-hydroxystilbamidine. Large amounts of these drugs were given to three of the six patients, one patient having received a total of 22.5 gm. of stilbamidine. More improvement appears to have been made with doses of 300 mg. of stilbamidine daily than with the conventional doses of 150 mg. per day. This is possibly explained by in vitro evidence of increased resistance of *B. dermatitidis* to stilbamidine.[13] No correlation could be made between the appearance of fifth nerve involvement and the total dosage of stilbamidine.

SUMMARIO IN INTERLINGUA

Es reportate in detalio le casos de 6 patientes con demonstrate blastomycosis nordamerican. Nos opina que omne iste casos representa exemplos de infection systemic ben que duo del inficite individuos non exhibiva positive signos clinic del involvimento de ulle systema altere que le pelle. Un de iste duo individuos habeva culturas positive del sputo. Studios pulmonar—includente bronchoscopia—non succedeva a demonstrar le foco del morbo. Le altere individuo deviava ab le forma usual de involvimento cutanee in tanto que ille disveloppava granulomas de membrana mucose.

Le 6 patientes esseva tractate con stilbamidina o 2-hydroxystilbamidina o un combination de ambes, e omnes esseva observate durante al minus un anno ante que illes esseva includite in le presente studio. Nos constatava nulle correlation inter le curation apparente e le amontas total del drogas administrate. Il existe indicationes que doses diurne de 300 mg de stilbamidina o 450 mg de 2-hydroxystilbamidina es plus efficace que le usualmente prescribite dosage de un medietate de iste amontas. In 3 del reportate 6 casos, le drogas combinate esseva administrate in quantitates total de 25,3 g, 17,6 g, e 20,925 g. Tamen, al tempore del redaction del presente reporto nos non pote considerar ulle de iste 3 casos como curate.

Il pareva exister un certe correlation inter le resultato del tractamento e le responsa immunologic que esseva obtenite. Quatro patientes habeva negative tests cutanee a blastomycina, e iste mesme patientes habeva etiam repetite recidivas post apparentemente succedite tractamentos. In 3 de iste 4 patientes nos executava studios de fixation de complemento. Le resultatos esseva positive, con titros significative. Nulle anticorpores fixante le complemento esseva demonstrate in le duo casos in que le tractamento resultava apparentemente in curation.

Toxicitate in le forma de alterationes sensorial del nervo trigeminal occurreva in 4 del 6 casos. Sed nulle correlation existeva inter le quantitate del droga administrate e le occurrentia de iste alterationes.

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CASE REPORTS

ADDISON'S DISEASE COMPLICATING DIABETES MELLITUS IN ADOLESCENCE *

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A survey of the literature fails to reveal documented cases of coexisting diabetes mellitus and Addison's disease below the age of 15. Addison's disease alone is a rare condition in childhood. A study of the disease in children was made by Russell and Potter [1] in 1951. They report only 66 cases of Addison's disease in children which they consider to be adequately substantiated. Diabetes mellitus is not mentioned as a complicating disease in any of these patients.

In 1943 Thorn and Clinton [2] reviewed the literature and found 11 authenticated cases in which Addison's disease and diabetes mellitus developed simultaneously, or in which the onset of the diabetes antedated Addison's disease. In four of these patients the Addison's disease and diabetes mellitus apparently developed at the same time; in the remaining seven, Addison's disease began after the onset of diabetes. Of all the cases, that presented by Simpson [3] in 1932 is the youngest. The patient was a 16 year old boy who developed Addison's disease and diabetes mellitus concomitantly. He had skin pigmentation and markedly elevated fasting blood sugars. He died shortly afterwards, and at postmortem atrophy of the adrenals as well as of the islets of Langerhans was found.

CASE REPORT

The patient we have had under recent observation was a white male who first manifested the symptoms of diabetes mellitus at the age of 10, and later, at 15, developed Addison's disease. He was born in 1937, a full term normal infant weighing almost six pounds. His growth was slow but no developmental defects were noted. There were occasional colds but no severe illnesses. Because of some weight loss he was taken to a physician who found sugar in his urine and referred him to the hospital. He was admitted for the first time to the Jewish Hospital of Brooklyn in December, 1947. At this time his weight was 50 pounds, the normal for a 10 year old being about 66 pounds. The remainder of the physical was not significant. A glucose tolerance test showed a typical diabetic curve. Tuberculin tests to 5.0 mg. were negative. A diagnosis of diabetes mellitus was made and he was placed on 25 units of protamine zinc insulin and a 1,900 calorie diet. For the next five years he was seen periodically. His fasting sugars varied between 84 and 289 mg. per 100 c.c. His insulin requirements gradually increased despite occasional attacks of clinical hypoglycemia. In October, 1950, he was changed to NPH insulin and in April, 1952, over four years after diabetes mellitus was detected, he was taking between

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75 and 80 units daily. About this time he developed a protracted cough which was considered to be pertussis. He made an uneventful recovery and physical examinations during convalescence were not remarkable. During this time diabetes mellitus was discovered in a younger sibling.

FIG. 1. Note pigmentation of the areolae and umbilicus, together with the well formed genitalia and abundant pubic hair.

A few months after his illness, however, he began feeling weak and cold, and had several insulin reactions. Insulin dosage was gradually decreased. At this time he complained of weakness in his legs. Soon after this he developed shortness of breath on exertion, and his mother noticed for the first time some tanning of the skin of his face. He was re-admitted to the Jewish Hospital in March, 1953, because of frequent vomiting for three days and persistent leg cramps.

At the time of physical examination in the hospital he complained of marked fatigue. He was only 58 inches tall and weighed 74 pounds. For his age these values are markedly below the limits of normal. There was moderate cyanosis of the lips and nails; pulse and blood pressure were not obtainable. Over the body was a diffuse brownish pigmentation, accentuated about the forehead, lips, areolae, genitalia and lower extremities (figure 1). No pigmentation of the buccal mucosa

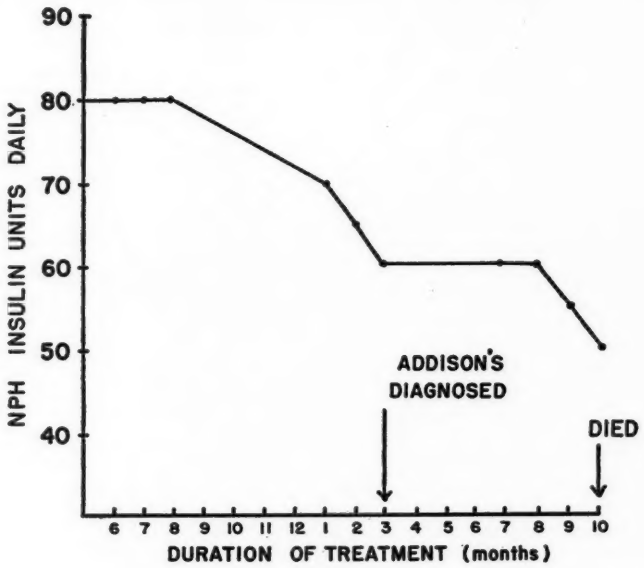

FIG. 2.

was present. Pubic and axillary hair was abundant, and the genitalia were well developed. The eyeballs were sunken but skin turgor was good. A pharyngitis was also present. Addison's disease was suspected and blood chemical studies were immediately made. These revealed a significant reduction in sodium and chloride, with an elevation of the potassium. The exact values were:

Na—128 mEq./L.
Cl — 81 mEq./L.
K — 6 mEq./L.

The blood sugar was 234 mg. per 100 c.c. and the CO_2 was 20.8 mEq./L. The urine showed sugar with a trace of acetone. The hemoglobin was 19 gm. per 100 c.c., and a blood smear showed 10% eosinophils. Four hours after instituting fluid

and electrolyte therapy the acetone had disappeared from the urine and the hemoglobin had fallen to 8 gm. per 100 c.c. However, an eosinophil count of between 7 and 10% persisted. With continuous therapy his clinical condition improved. He gradually became stronger and the exertional dyspnea lessened. On the following day a radial pulse could be felt and the blood pressure was 90/50 mm. of Hg. Shortly thereafter he was started on intramuscular desoxycorticosterone acetate in oil, 2.5 mg. daily. Throughout the remainder of his hospital stay the pulse and blood pressure continued stable and he was always alert and active. Electrolyte studies of his blood were made frequently. Except for a test period of two days, during which desoxycorticosterone was withheld and a low sodium diet given, the electrolytes were normal. During this withdrawal period there was no change in the clinical appearance of the boy, but the electrolytes varied. The sodium and chloride began to fall and the potassium became elevated. When steroid therapy and a regular diet were re-instituted, the electrolytes once again returned to normal.

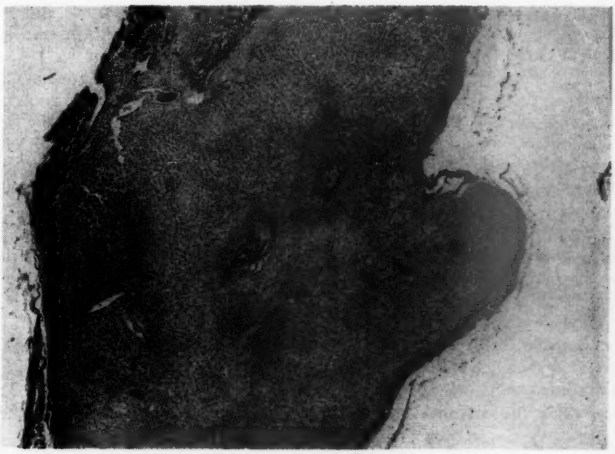

FIG. 3. Section of adrenal tissue showing absence of the cortical layers with lymphocytic infiltration and lymphoid follicles. × 40.

Three 17-ketosteroid determinations on the urine were done. Four days after admission a 24 hour specimen gave a value of 0.54 mg.; another 14 days afterward, 3.84 mg.; and the last, seven weeks later, was 7.36 mg. The first determination is markedly depressed; the latter two are still below normal according to our laboratory values. A four hour ACTH-eosinophil test was performed. The circulating eosinophil count before the administration of ACTH was 374/cu. mm. Four hours after 25 mg. of ACTH were given intramuscularly, the count was 253/cu. mm. Since there was less than a 50% fall in circulating eosinophils during this period, the test suggests impaired adrenocortical activity.[4]

Tuberculin tests continued negative. Electrocardiograms taken during the recovery phase were within normal limits. Chest x-rays showed normal lung shadows and a small heart. Skull and abdominal x-rays were negative.

The patient continued to improve and was discharged on 5 mg. of intramuscular desoxycorticosterone acetate three times weekly, supplemented by 9 gm. of sodium chloride daily.

His condition continued unchanged until four months later, when his mother noticed that the pigmentation was increasing and had spread to the gums. Two weeks prior to his third and final admission he developed pains in his legs and fatigue on exertion. His insulin requirements continued to decrease (figure 2). Six months before the diagnosis of Addison's disease he was taking 80 units daily. He began to have repeated attacks of hypoglycemia, and the dosage was gradually lowered to 60 units. Over the seven months following the diagnosis of Addison's disease he had an increasing number of insulin shocks and the dosage was further reduced. Several weeks prior to his last hospital admission it was necessary to lower it to 50 units.

With the onset of pains in his legs his condition quickly deteriorated and he was admitted to the hospital in a drowsy state. His skin was hot and dry, the nails were very cyanotic, and the pigmentation was especially prominent. The radial pulse was easily palpable, and the blood pressure was 100/68 mm. of Hg. The pharynx was markedly reddened and there was generalized lymphadenopathy. The urine showed no sugar or acetone. Blood electrolytes were normal, and the blood sugar was 72 mg. per 100 c.c. The boy was treated with fluids, electrolytes and adrenocortical extract, but death occurred 12 hours after admission.

Necropsy Findings: There were several small fragments of brownish tissue in place of both adrenals, lying close to the kidneys and admixed with fat and connective tissue. Microscopically there were groups of adrenal cells limited by a fibrous capsule. These cells were grouped in ovoids which were separated by connective tissue showing lymphocytic infiltration with lymphoid follicles (figure 3). The adrenal tissue was atrophic, with obliteration of the cortical layers. The architecture of the medulla was destroyed, only a few medullary cells being found. The anatomic diagnosis was primary atrophy of the adrenal glands.

The pancreas was grossly normal, but microscopically it showed a striking decrease in the number and size of the islets of Langerhans.

The general cellular pattern of the pituitary gland was well maintained. Study of the sections with hematoxylin and eosin stain showed a definite reduction in the number of basophil cells, with a corresponding increase in the chromophobe cells.

The testes were normal except for mild decrease in the number of mature sperm cells. Thyroid and parathyroid glands were normal. The thymus was large. The heart was small but not unusual, and the lungs showed no evidence of tuberculosis.

Discussion

This case is of unusual interest because it demonstrates the rare occurrence of disturbed function of two closely interrelated endocrine systems. It illustrates the clinical and metabolic changes that develop when two such deficiencies appear.

However, before making a diagnosis of primary disease of the pancreas and adrenals it was necessary to rule out a pituitary deficiency. Several clinical features of this case made such a diagnosis unlikely. With pituitary deficiency the gonadotropic functions are among the first to be affected. In males with this condition the testes are small and immature and sometimes there is cryptorchism. There is no spermatogenesis, and such secondary sexual changes as the growth of the penis fail to appear. There is a lack of adrenal and testicular androgen, the 17-ketosteroid excretion being less than 2 mg. per day, indicating a deficiency of both adrenal and testicular function. In addition, they exhibit no true Addisonian symptoms with evidence of failure of the electrolyte regulating factors.[5, 6]

In contrast, this patient had well formed genitalia and adequate pubic and axillary hair. At the time of his first admission in adrenocortical failure his 17-ketosteroids were very low. However, during convalescence they gradually rose. While this might be interpreted as a return of some adrenal function, the increasing pigmentation, muscle pains and asthenia which occurred subsequently do not support this view. However, temporary depression of testicular function during the episode of Addisonian crisis might explain in part the later rise in 17-ketosteroid production.

Finally, at post mortem there was no evidence of primary pituitary disease. Crooke and Russell [7] in 1935 observed in the pituitary glands of patients with Addison's disease a striking decrease in the number of basophils, with a corresponding increase in the number of chromophobe cells. Our patient showed similar changes. Thus all evidence supports the diagnosis of primary disease of the adrenal glands rather than of the pituitary.

If there is no single cause for this polyglandular deficiency, how may it be explained? It seems likely that the boy was predisposed to diabetes, since a younger brother has the disease. As for the adrenal failure, microscopic examination ruled out tuberculosis. The remaining possible causes of failure are hemorrhage, infection or primary atrophy of the adrenal. Adrenal hemorrhage at birth has been reported as a cause of serious adrenal destruction,[8, 9] but the boy was an easy delivery with no record of birth injury or neonatal distress. Infections have been found to cause destructive changes in the adrenal gland,[10] but at no time did he suffer any severe illness. There was one suspected attack of pertussis, but no signs or symptoms of adrenal failure were noted either during or immediately after the illness. The presenting symptom of weakness began several months later. It therefore seems unlikely that whooping cough could be solely responsible for such widespread damage to the adrenals.

It appears, then, that no known factor can be held responsible for the destructive process. The clinical diagnosis of primary atrophy of the adrenals was confirmed by pathologic examination. To find such a condition in a boy of 15 is most uncommon. Russell and Potter [1] found only two cases of atrophy in 56 cases of Addison's disease in the 10 to 15 year old group.

It is of interest to study the changing insulin needs of this diabetic boy after he developed Addison's disease. Thorn and Clinton tabulated the insulin requirements in six documented cases of diabetes mellitus who later showed Addison's disease. In four of these the insulin need decreased, one showed an improved glucose tolerance test and one required an increase in his dosage. Our patient had a definite decrease in his insulin needs with the onset of Addison's disease.

A prominent feature of this case was the eosinophilia which persisted during and following recovery from his initial crisis. While the effects of exogenous ACTH and corticosteroids upon the level of circulating eosinophils have been adequately demonstrated, no consistent changes in the blood eosinophil level have been shown in either children or adults with Addison's disease. Recently Deamer and Silver [11] observed eosinophilia in the blood of several children with adrenal insufficiency. Two of their patients showed eosinophilia only when salt and water metabolism were disturbed. In our case, however, the eosino-

philia persisted in the recovery phase when the blood electrolytes were normal. We have no explanation for this other than its being a manifestation of poor adrenocortical activity.

One final point of interest concerns the blood electrolyte pattern of this patient before death. The blood electrolytes in Addisonian crisis usually show low sodium and chloride levels with an elevated potassium. During his first Addisonian crisis this patient exhibited these changes. However, just prior to death two determinations revealed normal blood levels of sodium and chloride, with a normal blood sugar. Although uncommon, such conditions have been described. Soffer [12] mentions three patients with Addison's disease who died in crisis despite normal levels of blood electrolytes. The cause of death in these cases is unknown but may be due to unidentified adrenal cortical factors.

Summary

A case is presented of diabetes mellitus complicated by Addison's disease in an adolescent. The necropsy findings are described, together with the possible etiologic factors. The characteristic blood electrolyte disturbances, with their response to therapy, and the changing insulin needs in a diabetic after the onset of Addison's disease are demonstrated.

Acknowledgment

Acknowledgment is made to Dr. David Grayzel, of the Department of Pathology at the Jewish Hospital of Brooklyn.

Summario in Interlingua

Es presentate un caso de diabete mellite, complicate per morbo addisonian, in un adolescente mascule. Le symptomas de diabete mellite esseva primo manifeste al etate de 10 annos. Le morbo de Addison esseva detegite al etate de 15 annos. Esseva executate numerose studios hematologic. Illos demonstrava le typic alterationes electrolytic que se observa in morbo addisonian. Esseva etiam observate un elevation persistente del sucro sanguinee. Un grado de eosinophilia de inter 7 e 10 pro cento in le sanguine peripheric esseva presente durante e immediatemente post le prime crise del morbo addisonian. Un conto eosinophilic quatro horas post ACTH e plure determinationes de 17-cetosteroides confirmava le presentia de insufficientia adrenocortical. Post le declaration de morbo de Addison le patiente comenciava suffrer plus frequente attaccos de hypoglycemia clinic, e il deveniva necessari reducer su dosage de insulina ab 880 a 50 unitates per die. Le morbo de Addison esseva controlate per medio de acetato de disoxycorticosterona e tablettas de chlorido de natrium. Le patiente moriva 7 menses post le declaration del morbo de Addison. Le examine necroptic revelava nulle glandulas adrenal; esseva trovate solmente plure parve fragmentos de texito con un apparentia microscopic de texito adrenal. Le glandula pituitari esseva normal, excepte que illo monstrava un reduction del numero de cellulas basophile e un correspondente augmento del numero de cellulas chromophobe. Le diagnose anatomic esseva atrophia primari del glandulas adrenal con hypoplasia del cellulas del insulas pancreatic. Nulle signo de tuberculosis esseva constatate. Isto pare esser le plus juvene authentic caso usque nunc reportate de coexistente diabete mellite e morbo de Addison.

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ISCHEMIC NECROSIS OF THE LEGS AS A COMPLICATION OF COARCTATION OF THE AORTA*

By Marcus J. Zbar, M.D., *Nashville, Tennessee*

Introduction

An autopsied case of coarctation of the aorta complicated by ischemic necrosis of the legs prompted a review of the pertinent literature. No similar cases were recorded, and it was thought worth while to report the case with comment on the pathogenesis of the associated lesions. No detailed discussion of the signs and symptoms, pathologic findings or altered physiology in coarctation will be attempted except as pertinent to this particular case. Similar cases may be seen and diagnosed in the future if the possibility of a coexistent coarctation of the aorta is considered in cases of ischemic necrosis of the legs of obscure etiology.

Case Report

A 43 year old unmarried Negro female was admitted to Vanderbilt University Hospital on January 21, 1953, delirious and complaining of pain in the legs. The history as obtained from the family was of questionable reliability, but it was stated

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that she had been mentally retarded since childhood and for 30 years had had the habit of sitting so close to the fire that on numerous occasions the skin of the legs was actually blistered; as a result the pretibial skin had become extremely tough and scarred. Three months prior to admission she had developed edema of the lower extremities (the degree was not stated); this responded readily to pills administered by her private physician. Shortly before Christmas of 1952 large blisters again appeared on the legs. Constant "picking" at these blisters resulted in an infection, following which she spent most of the time in bed. Two weeks prior to admission she

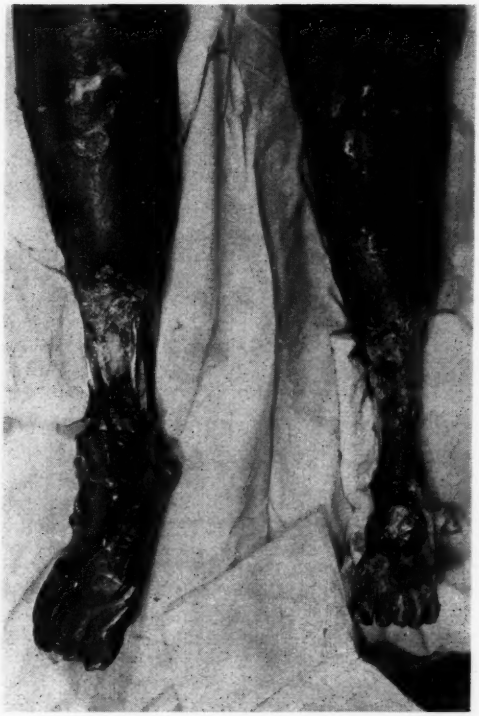

FIG. 1. Appearance of legs at time of admission. Note extreme bilateral changes.

was confined to bed, and one week prior to admission, after being refused permission to get out of bed, she had a "temper tantrum," kicking at the wall with sufficient severity to dislodge bits of flesh from the legs. Eight days later she was admitted to the hospital.

Physical Examination: Temperature, 98° F.; pulse, 120/minute; respirations, 30/minute; blood pressure, 142/76 mm. of mercury (in which arm was not stated, and at no time was the blood pressure in the legs recorded). She was irrational and in acute distress. There was generalized edema, especially in the dependent areas. Scattered 1 to 2 mm. maculopapular lesions were noted over the face. The skin of

both arms was hyperkeratotic, and the left hand was swollen and indurated. There was no significant lymphadenopathy. Extreme gangrenous changes were seen to involve both legs (figure 1), the tissue being absent from the lower third, exposing the bony structures and tendons. The feet were mummified, but the skin was intact. Ophthalmologic examination was not remarkable. The chest was symmetrical, and the interspaces retracted slightly with inspiration. The breath sounds were clear, although scattered basilar râles were audible. There was cardiac enlargement upon percussion. The pulse was rapid and weak. The rhythm and rate were regular. There was an apical systolic murmur obliterating the first heart sound and extending up to the second heart sound. In addition, a to-and-fro friction rub was heard to the left of the sternum. The abdomen was distended and tense. The neurologic examination was not remarkable. A note placed on the chart after the patient had died stated that one examiner had been unable to palpate the abdominal aortic or femoral pulsations; this was attributed to the anasarca.

Hospital Course: Approximately one and one-half months elapsed from admission until death, and although there was considerable speculation as to the basic etiology of the ischemic necrosis of the legs, no definite etiologic diagnosis was determined. On the fourth day the temperature spiked to 107° F. (rectally), but by the next day had dropped to 95° F. (rectally). Such marked temperature swings were frequently noted, on some occasions variations of six or seven degrees occurring during a 24 hour period. A gallop rhythm developed during the first week which responded readily to digitalization.

Initial treatment consisted of cleaning and dressing the wounds, and the administration of antibiotics. On the sixth day a bilateral supracondylar amputation was performed without difficulty, and the left hand was incised and drained. Pathologic examination of the legs revealed extensive gangrenous changes. The popliteal arteries were thickened and the peroneal arteries contained thrombi.

Postoperatively the temperature spiking continued, and the patient remained irrational and delirious, and often screamed. The stumps healed poorly, and were always covered with a thick, purulent exudate which, when cultured, revealed an anerobic streptococcus and a coliform bacillus, both sensitive only to chloramphenicol, which was added to the antibiotic regimen. Although the urine output remained good, facial and periorbital edema were frequently noted, and on many occasions coarse râles were present over the lung fields.

Three weeks after admission a tracheotomy was performed because of respiratory difficulty. The blood pressure, which had averaged 150/75 mm. of mercury earlier, rose to 176/94 mm. of mercury. By this time the anasarca had cleared and extreme emaciation was apparent. Subsequently the course remained essentially unchanged. There was almost constant hyperpyrexia, often up to 105° F. (rectally), and on March 8 she died.

Autopsy

Gross Examination: Autopsy was begun approximately three hours post mortem. External examination revealed considerable emaciation and poor tissue turgor; shotty nodes were palpable in the left axilla and in the inguinal regions, and there was a large decubitus ulcer over the left buttock. There was a tracheotomy incision showing early healing. Tissues of the dorsum of the left hand were indurated and darkened. The hand was swollen and edematous, and in the midportion there was an umbilicated, healing 2 cm. surgical incision. Marked restriction of movement of the metacarpophalangeal joints was apparent on the left. The face was puffy and the site of irregularly scattered, 1 to 2 mm., brawny maculopapular lesions. The chest was symmetric, with bilateral resonance; the abdomen was distended and tympanitic. The genitalia were normal female. The lower extremities had been amputated above

the condyles; the stumps showed poor healing and were covered with a thick, greenish yellow exudate. The severed ends of the femora were covered by what seemed to be healthy granulation tissue, and the surrounding skin was freely movable circumferentially. When the body was opened there was evidence of marked weight loss, and the musculature was pallid and edematous. Neither the pleural nor the peritoneal cavities were remarkable. The heart was enlarged in situ, the cardiac-thoracic ratio being 15 to 23 cm. An irregularly scattered, partially organized fibrinous exudate was noted on the visceral and parietal pericardium.

The heart weighed 380 gm. The coronary arteries were slightly atherosclerotic but were patent throughout. The left ventricular myocardium was coarse and meas-

FIG. 2. Appearance of internal aspect of aorta. Note obstructing wedge and posterior aspect of thinning. The markedly stenotic orifice of the left subclavian artery (at the apex of the thinned area) is also well shown.

ured approximately 20 and 13 mm. in thickness at the base and apex, respectively. The aortic valve measured 5.5 cm. in circumference. The cusps were slightly thickened but were otherwise normal. The remainder of the heart was nonrevealing.

The aorta arose normally and pursued a normal course. From the lower thoracic portion distalward, it was elastic and showed no pathologic alterations. As the upper portion and arch were opened, a firm, circumferentially arranged, almost complete obstruction was encountered approximately 4 cm. distal to the orifice of the left subclavian artery (figure 2). This obstruction was actually a ridgelike structure

which was deficient posterolaterally for a width of approximately 3 to 4 mm. In this region the aortic wall was thin; this narrow zone of thinning extended cephalad for 3.5 cm., and bulged outward slightly. The ridge had a wedgelike shape, the apex directed toward the aortic lumen and the base arising from the intimal aspect of the aorta. Grossly, it appeared to be composed of hyalinized fibrous tissue; it cut with some difficulty, and was gritty. The innermost aspect of the elevation was slightly irregular but there were no accretions. The intimal aspect of the aorta above the obstruction was mottled, irregular and wrinkled, especially anteriorly and posteriorly, and there were small, scattered atheromata. The aortic lamellae both above and below the ridge could easily be separated. The obstruction itself reduced the aortic lumen to a caliber of not more than 2 or 3 mm. The aortic intima distal to the obstructing lesion, although similar to that above, was not so severely involved. Lateral and 2 cm. distal to the aforementioned defect in the ridge there was a small, roughly ovoid, thin aneurysmal outpouching which measured about 0.7 by 0.5 cm. and about 0.4 cm. deep. The aorta composing this aneurysm was quite thin, and the sectioned surfaces of the wall of the aorta proximal and distal to the ridge revealed what appeared grossly to be the media continuing for a slight distance and then disappearing. At the points where the medial tissues disappeared there were striking proliferation and thickening of the subintimal tissues, these changes corresponding to the above described areas of irregularity encountered on the intimal aspect of the aorta. The wall of the arch also was thickened. The innominate and left common carotid arteries arose from a common trunk, the orifice of which was 9 cm. in diameter. Approximately 1.7 cm. distal to this point was the orifice of the left subclavian artery, which measured about 1 by 2 mm. in diameter, the vessel being partially occluded at its origin by a very thick, rather wide mass of fibrous tissue arising from the posterior aspect of the aortic wall in the region of the orifice of the left subclavian artery. Distal to this area the artery was of essentially normal caliber, although its wall was slightly thickened. At no point was there evidence of collateral circulation.

The remainder of the autopsy was essentially nonrevealing except for passive congestion of the liver and old, incompletely occluding thrombi in two of the arteries of the left lower lobe. The brain and kidneys were normal.

Microscopic Notes

Heart: The myocardial fibers were moderately hypertrophied, with some "boxing" of the nuclei. Small, scattered areas of remote scarring were seen, and there was some interstitial edema, especially perivascularly. The small arteries were not remarkable, and no changes were seen in either the epicardium or the endocardium.

Sections from the viscera other than the aorta were essentially not remarkable. The walls of the smaller pulmonary arteries were thickened, and scattered small veins contained thrombi. Occasional hyaline thrombi were seen in the alveolar septal capillaries. Acute congestive changes were seen in the liver and spleen; the kidneys and central nervous system were normal.

Aorta: Numerous sections of the aorta from all areas were studied. These were stained with hematoxylin and eosin as well as with Mallory's aniline blue and Weigert's elastic tissue stain.

The section from the abdominal aorta was microscopically normal.

The remainder of the sections taken from above and below the zone of coarctation, the coarctate area itself, and from the small aneurysm below the coarctate zone were in many respects similar, the changes varying essentially in degree. Generally, the most striking change was in the subintimal collagenous tissue. There was marked, diffuse proliferation of these tissues with extensive hyalinization. Atheromata were

small and infrequent. There were scattered, small zones of what appeared to be degenerative change within this hyalinized tissue, and occasional small, irregular vascularized scars in which there was an infiltration of chronic inflammatory cells, including plasma cells. The intimal aspect of this thick collagenous layer was irregular but devoid of thrombi. The sections from the zone of coarctation itself revealed the obstruction to be composed also of dense, hyalinized collagenous tissue. This faded out rather strikingly posteriorly over the area of the grossly described valley. This extreme proliferation of the subintimal tissue continued cephalad throughout its grossly described course. An occasional small atheroma was seen in the proliferated subintimal tissues surrounding the orifice of the left subclavian artery. In addition, in this region there was a small focus of calcification which encroached upon and resulted in considerable distortion and degeneration of the underlying media. An interesting observation throughout was the presence of numerous engorged, usually fair-sized vascular channels located in either the deeper layers of the thickened subintimal tissue or at the line of junction of this tissue with the media itself. Elastic tissue stains showed an irregular scattering of elastic fibrils throughout the thickened subintimal layer. The basic collagenous nature of this layer was established with collagenous tissue stains.

The media was amazingly well preserved throughout. Small focal areas of medial scarring and degeneration were seen, and there was moderate vascularization of these areas, along with an infiltration of round cells and plasma cells. In some areas the medial lamellae appeared loose. At the base of the small aneurysm, marked medial destruction was seen, in some points the tissue being almost totally destroyed. Plasma cell infiltration into this particular zone, however, was minimal. This same destructive change was noted in the section from the orifice of the left subclavian artery, especially beneath the abovementioned focus of calcification. The media continued relatively intact beneath the coarctate zone; there was no evidence of medial contribution to the formation of the obstructing lesion.

The adventitia in all sections save that from the abdominal aorta showed changes compatible with moderate syphilitic damage. The adventitial tissues throughout showed conspicuous proliferation and scarring, with scattered areas of hyalinization. At one point a small area of what appeared to be degeneration of the hyalinized scar tissue was noted. A diffuse, heavy and usually perivascularly arranged infiltration of lymphocytes and plasma cells was seen, and rather marked intimal proliferation was noted in most of the adventitial arteries; some revealed marked diminution in caliber. A single large artery, probably an intercostal vessel, showed similar but less marked intimal changes.

Discussion

In an extensive review of the reported cases of coarctation of the aorta none was encountered resembling this one, although there were several in which there was mention of either edema of the lower extremities or intermittent claudication, or both.[1, 2, 4, 5, 6, 8] It is well known that coarctation of the aorta may be associated with either atresia or stenosis of either subclavian artery,[13] but in the studied literature there was no mention of difficulties similar to those involving the left hand as in this case.

It is interesting that collateral circulatory channels were not demonstrated by x-ray or at postmortem examination, and there was no evidence of their prior existence. We are at a loss to explain their absence. Although collateral circulation is usually present, it is not invariably demonstrable.[2, 7, 13] The collateral circulatory channels vary from case to case,[12] and even in the same case on the two sides of the body, depending upon the site of the area of coarctation.

Characteristic notching of the ribs is seen on x-ray examination in only approximately 25% of cases of coarctation of the aorta.[12] It is possible that in this case the degree of aortic stenosis during early life was insufficient to demand the development of a collateral circulation. An interesting finding was the presence of fairly large intramural vascular channels within the deeper portions of the thickened aortic intima.

A diagnosis of coarctation of the aorta was not entertained in this patient prior to death. The blood pressure was never taken in the legs or in both arms, as far as can be learned from the clinical record. However, the appearance of the aorta and the left subclavian artery makes it very likely that significant blood pressure variations existed in these sites. Appreciable differences in the blood pressure in the arms was seen in only 10 out of 175 cases of coarctation of the aorta, and in nine of these the pressure was higher on the right.[14] King suggested that the blood pressure variations in these cases were due to involvement of either the aortic isthmus or the orifice of the left subclavian artery. Marked hypotension in the left arm is rare. The blood pressure in this patient prior to her hospital admission is not known. The presence of long-term hypertension is suggested by a heart weight of 380 gm., even after prolonged bed-rest. Microscopically, enlargement of the myocardial fibers and "boxing" of the nuclei also indicate myocardial hypertrophy. There is, however, apparently little correlation between cardiac weight and the degree of coarctation.[5, 9, 11]

The abnormalities of the aorta in this case must have been congenital. It is conceivable that the lesion might have been acquired, but its location and general configuration are certainly typical of the congenital deformity. The indentation of the aortic wall at the site of the coarctation was not so apparent as that usually described, and the channel through the obstruction was in a posterolateral situation rather than in the region of insertion of the ligamentum arteriosum. Otherwise, the wedge-shaped structure causing the stenosis was generally similar to those previously described. The medial elastica, however, did not participate in the formation of the wedge, in contrast to the findings in all cases of coarctation of the aorta studied by Edwards et al.[12] The intimal thickening described by these authors at the zone of aortic narrowing and said to be present in specimens from adults and adolescents was strikingly shown in this case.

Undoubtedly, bilateral ischemic necrosis of the legs is a rare complication of coarctation of the aorta. Two cases reported by Pelletier in 1828 developed a "phlegmon" of the lower extremities at the site of a venesection, and Mackenzie in 1927 reported a case of a child with coarctation of the aorta who developed edema, petechiae and furuncles of the lower limbs secondary to bacterial endocarditis involving the coarctate area. The presence of syphilitic aortitis in our case is interesting, and the changes developing apparently secondarily to that disease are unique. Extensive adventitial change was the main syphilitic stigma; the media throughout was well preserved, with only small focal areas of degeneration. The marked subintimal collagenous tissue proliferation and hyalinization are probably secondary to the syphilis. The insignificant medial involvement with massive subintimal scarring is unusual in syphilis. It might be postulated that the degree of vascularity of the deeper subintimal layers facilitated

the development of syphilitic damage here rather than within the media. Furthermore, the subintimal proliferative changes must have augmented the obstruction to blood flow, as the most marked proliferative changes were superimposed on the obstructing ridge itself. The small aneurysm distal to the obstruction probably resulted from a combination of syphilitic mesaortitis plus the lateral pressure exerted by the blood distal to the constriction (Bernoulli effect).

Recent studies have shown that at rest there is little difference in blood flow to the lower extremities in individuals with and without coarctation of the aorta, in contrast to previous opinion.[2, 3, 10, 12] However, individuals with coarctation meet demands for increased blood flow poorly.[3] Such a "functional difference" might well have been operative in this case. Severe coarctation of the aorta and prolonged trauma to the legs with inadequate collateral circulation might well have initiated the development and facilitated the progression of the ischemic changes when additional demands such as infection and congestive heart failure were superimposed.

Summary

A case is presented of coarctation of the thoracic aorta in a 43 year old Negro woman, associated with bilateral ischemic necrosis of the lower extremities. The aorta also exhibited marked subintimal scarring which was secondary to syphilitic aortitis and which augmented the obstructive effect of the coarctation. A possible mode of pathogenesis for the changes found in this case is presented.

Summario in Interlingua

Es presentate un caso de coarctation del aorta, non suspectate ante le morte, e complicate per necrosis ischemic del gambas. Le patiente esseva un negra de 40 annos de etate. Durante multe annos illa habeva habite le habitude de exponer su gambas al calor del camino usque al disveloppamento de marcate cicatrisationes pretibial. Finalmente un tal exposition del gambas resultava in vesication con subsequente infection e hospitalisation. Decompensation cardiac se disveloppava apparentemente durante iste maladia, e le patiente esseva tractate per su medico private pro congestive disfallimento cardiac. Al admission al hospital illa delirava. Illa esseva anasarcose e habeva extreme lesiones gangrenose involvente le tertio inferior de ambe gambas. In despecto de amputation e extense e prolongate therapia, illa moriva circa un e medie menses post admission al hospital.

Al autopsia, le constatationes essential se trovava in le aorta. Le corde esseva moderatemente hypertrophiate. Il habeva un marcate coarctation del aorta, distalmente al origine del sinistre arteria subclavian, e le orificio de iste arteria esseva multo stenotic. Esseva apparente al sito del coarctation e supra illo marcate spissification e cicatrisation del pariete aortic, specialmente in le stratos subintimal. Le spissification esseva deficiente posterolateralmente in un area in que le pariete aortic esseva tenue e cannellate. Un parve aneurysma se trovava in un sito immediatemente distal al sito del coarctation. Nulle circulation collateral esseva demonstrabile. Ab le puncto de vista microscopic, le spissification e hyalinisation del pariete aortic e del texitos subintimal esseva debite tanto al congenite processo producente le coarctation como etiam a aortitis syphilitic. Esseva etiam notate un interessante, satis marcate vascularitate del plus profunde texitos subintimal.

In iste caso le pathogenese del necrosis ischemic del gambas non es completemente comprendite. Nulle comparabile casos esseva trovate in le litteratura. Nos opina que le repetite cicatrisation del gambas reduceva lor influxo de sanguine a un grado sufficiente pro causar necrosis ischemic quando nove requirimentos se presen-

tava, como per exemplo le requirimentos del infection e del congestive disfallimento cardiac, specialmente in le presentia de sever coarctation del aorta e de inadequate circulation collateral.

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RUPTURE OF AORTIC VALVE CUSP ATTACHMENT DUE TO CYSTIC MEDIONECROSIS OF THE AORTA: A CASE REPORT WITH NECROPSY FINDINGS*

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RUPTURE of the aortic valve is an infrequently reported condition despite the variety of causes.[1, 2, 3, 4, 5, 6, 7, 8] In the majority of instances the etiology is valve damage as a result of syphilis, bacterial endocarditis or arteriosclerosis, unless there is a history of specific external trauma. A few reports[1, 2, 3, 4] are found in which rupture of the valve occurred spontaneously or after varying degrees of physical exertion. In the case reported below, rupture of the com-

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missural attachment of the posterior and right anterior cusps of the aortic valve was found to be due to cystic medionecrosis of the aorta. A review of the literature in the English language did not reveal the previous association of these conditions.

Cystic medionecrosis was first described by Gsell and Erdheim and is usually associated with dissecting aneurysm of the aorta.[9, 10, 11, 12] The condition, which occurs predominantly in men, is most often described in older age groups, but there have been numerous reports of medionecrosis in younger individuals.[13, 14] The etiology and pathogenesis of the disease are at present unknown. Some workers [15] believe interference with vascularization of the media is the essential pathogenic mechanism. Schlichter [16] has experimentally produced in dogs changes typical of medionecrosis by searing the adventitia of the aorta. Recent investigators [11, 13, 17] have differentiated two types of medionecrosis: one involves the elastic tissue and occurs in young individuals, the other affects muscle tissue and is found in older persons. Cases are seen in which a combination of the two types is present. Differences in the histologic appearance of the lesion have been discussed since the earliest reports,[9, 18] but only recently has a clear relation become apparent between age and type of lesion.

Case Report

A 27 year old Negro male truck driver was admitted to the Veterans Administration Hospital, Jackson, Mississippi, on January 25, 1954, complaining of dyspnea of abrupt onset one month earlier. While visiting at the house of a friend he suddenly experienced in the upper abdomen and chest a sensation of fullness accompanied by choking, coughing and dyspnea. At that time he coughed up some blood-tinged sputum. Upon consulting his local physician he was told that he had "pneumonia and heart trouble," and was asked if he had noticed a "buzzing" in the chest. The patient became conscious of this noise only after it was called to his attention. He was given two injections, the nature of which was unknown to him. The cough subsequently improved but the dyspnea progressed, causing the patient to seek hospitalization. At the time of admission he complained of dyspnea on slight exertion and episodes of paroxysmal nocturnal dyspnea. There was no history of chest pain, recent hemoptysis or edema. He thought that he had slight fever at the time of onset but no chills. Other than the fever, there were no symptoms suggestive of rheumatic fever. No history of syphilis could be elicited.

Physical examination revealed a well developed and well nourished Negro male. The lungs disclosed no abnormalities. The heart was greatly enlarged to the left, and the point of maximal impulse was in the sixth intercostal space almost at the anterior axillary line. A systolic thrill was felt at the aortic area and an intense diastolic thrill along the left sternal border and at the apical area. Auscultation disclosed tachycardia, a regular rhythm, and a short systolic and a loud harsh diastolic murmur at the apex. A loud blowing diastolic murmur was present to the left of the sternum and in the aortic area. There was a short, rather harsh systolic murmur at the aortic area. The aortic second sound was not heard. The blood pressure was 116/56 mm. Hg in both arms. There was diminution of the radial pulses with the arms raised above the head. The liver was neither palpable nor tender; there was no edema. The remainder of the physical examination was not remarkable.

Laboratory Data: On admission the blood hemoglobin, leukocyte count and differential and urea nitrogen were all within normal limits and remained so during the course of hospitalization. The sedimentation rate (Wintrobe) was 32 mm. per

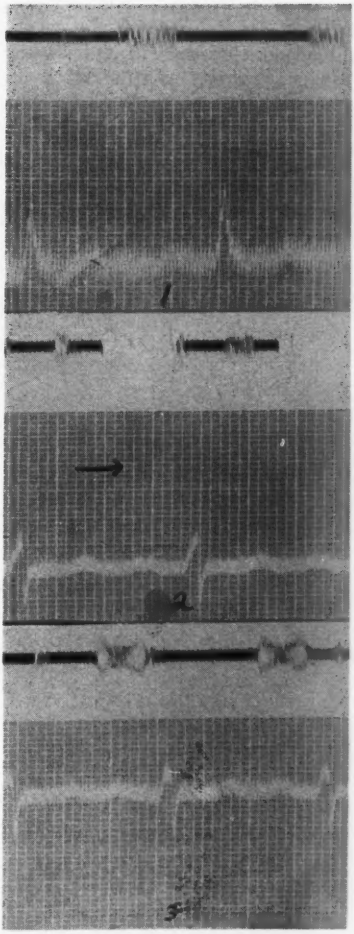

FIG. 1. Phonocardiogram. Tracing No. 1 over the right second interspace close to the sternum reveals the harsh diastolic murmur obtained during a period of cardiac decompensation. Tracing No. 2 over the same area taken during a period of relative cardiac compensation reveals the loud musical diastolic murmur. Tracing No. 3 taken from left shoulder demonstrates a decrescendo-crescendo musical murmur.

hour on admission; it fell to 8 mm. per hour one month later, but rose to 30 mm. per hour just prior to death. The only abnormality of the urine on admission was a 1 plus albumin; two weeks later there was also a slight pyuria. Repeated serologic examinations for syphilis were negative. Blood cultures with penicillinase revealed no growth. No sickling of the erythrocytes could be demonstrated.

X-ray examination of the chest disclosed congestive changes in the lung fields

and gross cardiac enlargement. There was marked prominence of the left cardiac border; the aorta was widened, elongated and tortuous. The electrocardiogram was compatible with left ventricular enlargement. There was a first degree AV block. Repeated tracings showed digitalis effects but no other significant changes.

Course in Hospital: Shortly after admission the patient developed signs of left ventricular failure. Circulation time (Decholin, arm-to-tongue) averaged 44 seconds; venous pressure was 180 mm. of H_2O. He was given digitalis and mercurial diuretics. There was decrease in the dyspnea and the patient became ambulatory.

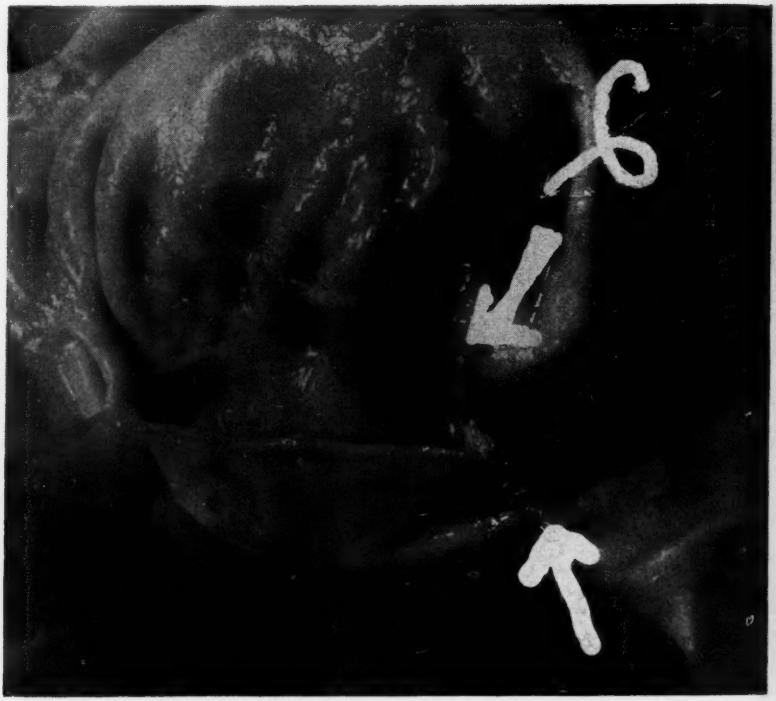

FIG. 2. Torn commissural attachment from aortic ring. Upper arrow indicates site of tear from aorta. Lower arrow points to the sagging free border of the involved cusps into the aortic valve opening. Above the level of the aortic ring a roughened area is visible in the first part of the aorta.

Eight days after admission the patient developed a spiking fever of 100° F. and was found to have a left otitis media, for which he received procaine penicillin twice daily for 10 days. The fever disappeared after two days and there were no symptoms referable to the ear after five days. With a maintenance dosage of digitalis there was continued improvement in the degree of cardiac compensation. Examination during a period when there was no evidence of cardiac decompensation revealed a loud musical diastolic murmur in the aortic area (figure 1). This murmur was present on repeated examinations so long as the patient exhibited no evidence of

cardiac decompensation, but as left ventricular failure became less well controlled the musical quality of the murmur was heard only when the patient was in the erect position. As the cardiac failure became intractable, the musical quality was lost and the murmur became harsh. The patient died on the seventy-sixth hospital day, approximately three months after the onset of symptoms.

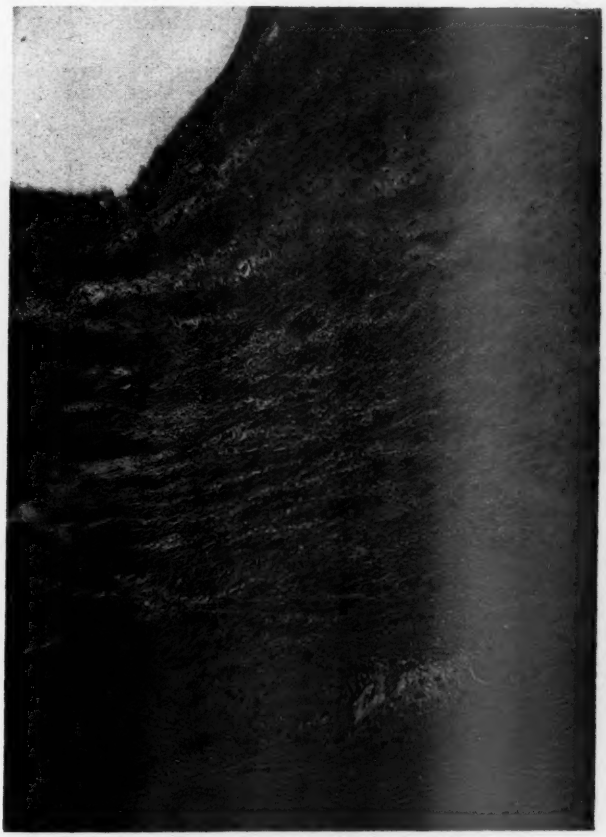

FIG. 3. Photomicrograph of aortic wall at site of torn commissural attachment. Typical change of cystic medial necrosis can be seen throughout section. (× 100.)

Autopsy Findings: The important findings were limited to the heart and the aorta. The lungs, liver and spleen revealed congestive changes grossly and microscopically, but the remainder of the organs were not remarkable. The central nervous system was not examined.

Heart: The heart was enlarged, weighing 730 gm. There was dilatation of the left ventricle with flattening of the papillary muscles. The left ventricular wall

measured 1.8 cm., the right 0.7 cm. The circumference of the aortic ring was 9.5 cm. The mitral and tricuspid valves were normal in appearance. The common attachment of the posterior and right anterior aortic valve cusps had separated from the site of insertion in the aorta (figure 2). The site of rupture on the aortic wall appeared smooth and healed over. Because of the loss of attachment, there was sagging of the free border of the involved cusps, with rolling of the ruptured attachment toward the center of the aortic valve opening. The protruding ruptured

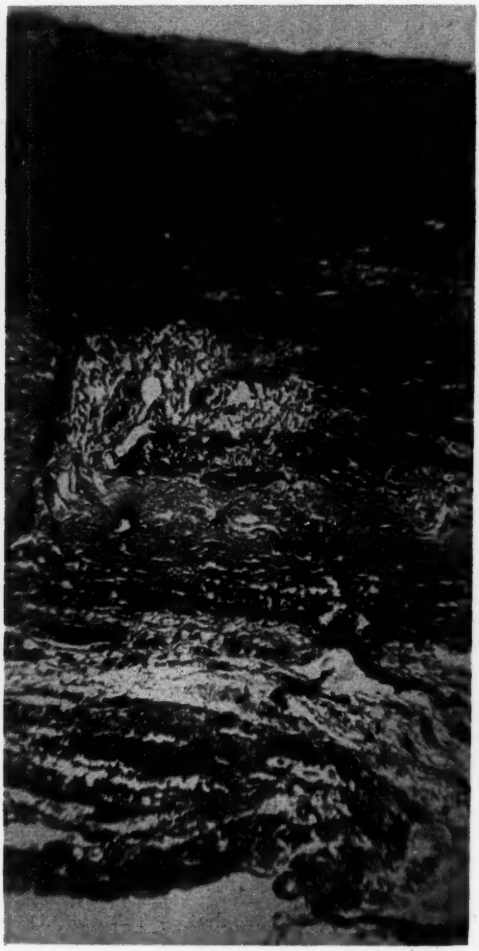

FIG. 4. Verhoeff's stain of aorta for elastic fibers. Distortion and destruction of elastic tissues are prominent throughout the section. (× 80.)

commissural attachment measured 5 mm. in length. The aortic valve cusps were intact and normal in appearance. The coronary arteries were patent and normal in appearance. Microscopic sections of the heart muscle revealed swelling of the fibers and muscle cell nuclei.

Aorta: The aorta measured 5 cm. in circumference at the arch and 6 cm. at the diaphragm. There was an irregular area of scarring, beginning just above the aortic ring and extending distally for 8 cm., which involved the entire circumference of the aorta (figure 2). No ulceration was present in this area, and elsewhere the intima was normal in appearance. Microscopic sections of the aorta in the area of the torn valve attachment revealed destruction of the elastic tissue (figure 3). Cystic degeneration was evident. Sections from the area of scarring at the root of the aorta showed thickening of the wall, due predominantly to increased thickness of the adventitia and the media (figure 4). The adventitia was edematous, and a mild chronic inflammatory process was present. Numerous thin-walled vessels penetrated into the media from the adventitia. The degeneration of the media with vacuolation of the muscle fibers was conspicuous. Chromotropic substance was seen in special stains, as were loss and separation of elastic fibers.

Comment

The sudden onset of dyspnea, fullness in the chest, cough, hemoptysis and the presence of a loud aortic diastolic murmur and diastolic thrill in this previously healthy individual constituted the typical findings of a ruptured aortic valve. The absence of pain at onset was unusual. The etiology of the aortic valve disease was not apparent until postmortem examination.

The appearance of a musical quality in the aortic diastolic murmur led to considerable speculation concerning the etiology of the aortic insufficiency in this patient. Gelfand and Bellet [8, 19] in their studies of musical aortic diastolic murmurs list the most frequent causes as (1) retroversion of an aortic leaflet in the course of syphilitic or, rarely, rheumatic aortic insufficiency; (2) bacterial endocarditis, or (3) rupture of an aortic cusp occurring spontaneously or following trauma. In their experience, the development of a musical murmur in the course of bacterial endocarditis was rare; nevertheless, this diagnosis was considered likely because the murmur changed character rapidly and frequently. The rapid changes were thought to be explained best by fibrin strands protruding into the regurgitant stream and then breaking off. At necropsy, however, there was no ulceration or fibrin at the site of the valve detachment on the aortic wall or about the protruding common attachment (figure 2).

The murmurs discussed by Gelfand and Bellet varied in intensity and musical quality in the same patient from day to day. There was no mention in their reports or those of others [2] of the disappearance of the musical quality with changes in the position of the patient. On occasions when the patient changed from the erect to the supine position the musical quality disappeared. The explanation of this finding is not definitely understood but may have been due to effects of gravity on the valve cusp or changes in the direction of the regurgitant stream. Changes in the quality of the murmur occurring over a period of days could be correlated with the degree of left ventricular failure. When the signs of left ventricular failure were present the murmur was loud and harsh, but it became musical with improvement in cardiac compensation. Apparently the change in the quality of the murmur was caused by varying

tensions on the free edges of the cusps and torn attachment. It is believed that the variation in tension was the result of dilatation and contraction of the aortic ring with fluctuation in the degree of left ventricular failure.

Howard [1] in 1928 reported a case of nontraumatic rupture of the aortic valve in a chauffeur who had sudden onset of dyspnea while cranking an automobile. The photograph of the heart and the gross necropsy report revealed changes strikingly similar to those in our patient. The microscopic report states only that the vasa vasorum showed no evidence of syphilis. No mention was made of defects in the aortic wall, but Howard's case was reported prior to the description of medionecrosis.

According to recent reports,[20, 21, 22, 23] cystic medionecrosis of the aorta is not uncommon in cases of arachnodactyly (Marfan's syndrome). Our patient was tall (72 inches) and rather thin, with a prominent forehead and deep-set eyes, but had no other stigmata of the syndrome. Bean [6] reported a case in which the clinical diagnosis of rupture of the aortic valve was made but not proved by necropsy. Because the patient had bilateral dislocation of the lenses, Bean considered an incomplete form of arachnodactyly, but the definite diagnosis was not made.

Microscopic changes seen in the aorta of our patient revealed a combined type of medionecrosis, since both the muscle fibers and elastic tissue were involved. There are numerous reports [13, 14, 15, 21, 22] of the association of known congenital abnormalities and the type of medionecrosis in which the destruction of elastic tissue is prominent. This association gives support to the belief that medionecrosis occurring as a result of destruction of the elastic tissue of the aorta is a congenital lesion.

Summary

A unique case, established by necropsy, is presented in which rupture of the commissural attachment of aortic valve cusps resulted from cystic medionecrosis of the aorta. The clinical manifestations were those of aortic insufficiency, which was associated with a changing musical aortic diastolic murmur, and of intractable left ventricular failure.

Summario in Interlingua

Es describite un caso de spontanee ruptura de un attachamento cuspidal de un valvula aortic, occurrente in un masculo negre de 27 annos de etate. Quatro septimanas ante su admission al hospital le patiente experientiava un sensation de plenitude in le thorace e le abdomine superior, accompaniate de suffocation, dyspnea, tusse, e hemoptysis. Durante le integre curso del morbo il non habeva dolores thoracic. Le entrata al hospital esseva motivate per progressive dyspnea nocturne paroxysmal e post effortio. Le patiente non habeva un historia de febre rheumatic o de syphilis. Le anormalitates revelate per le examine physic esseva restringite al corde que esseva multo allargate sinistrorsemente. Un fremito systolic esseva sensibile in le area aortic e un intense fremito diastolic al longo del margine sternal e in le area apical. Le auscultation revelava murmures systolic al apice e al base e un murmure diastolic al apice. Un forte e sufflante murmure diastolic esseva presente al sinistra del sterno e in le area aortic. Le pression sanguinee esseva 116/56 mm Hg. Le examines laboratorial non esseva remarcabile.

Un interessante characteristica clinic esseva le disveloppamento de un musical aortic murmure diastolic que dispareva e fluctuava con variationes in le grado del

compensation cardiac e con alterationes in le position del patiente. Le patiente moriva le 76te die de su sojorno al hospital. Ille habeva disfallimento sinistroventricular.

Le importante constatationes autoptic esseva restringite al corde e al aorta. Le attachamento commun del posterior e dexteroanterior cuspides del valvula aortic esseva separate ab le sito de lor insertion in le aorta. Le cuspides del valvula aortic esseva normal in lor apparition. Il habeva un area irregular de cicatrisation que involveva le integre circumferentia del prime portion del aorta. Microsectiones del aorta in le area del disrumpite attachamento valvular e del cicatrisation revelava medionecrosis que afficeva le elementos tanto muscular como etiam elastic. Iste caso representa un nove etiologia de ruptura del valvula aortic.

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COEXISTENT IDIOPATHIC HYPOPARATHYROIDISM AND PERNICIOUS ANEMIA IN A YOUNG GIRL: CASE REPORT *

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Idiopathic hypoparathyroidism is a rare disease beginning more often in childhood or adolescence. In 1952 Steinberg and Waldron[1] reviewed 51 cases of idiopathic hypoparathyroidism and reported an additional case. They adhered to the criteria established by Drake et al.:[2] (1) low serum calcium; (2) serum inorganic phosphorus greater than 5.0 mg. per 100 ml. in adults and 7.0 mg. per 100 ml. in patients aged 16 years and younger; (3) absence of renal insufficiency; (4) normal bones by roentgenogram to exclude infantile rickets or adult osteomalacia as the cause of hypocalcemia; and (5) chronic tetany. Of these 52 cases, 36 occurred in the first two decades of life, with no predilection for either sex.

Addisonian pernicious anemia has been reported even more rarely in children. A deficiency state characterized by a macrocytic anemia with megaloblastic bone marrow, pernicious anemia results from faulty absorption of vitamin B_{12} in the absence of the intrinsic factor of Castle contained in the normal gastric secretion. The presence of free hydrochloric acid does not exclude the diagnosis of pernicious anemia if it can be shown that intrinsic factor is nonetheless lacking.[3,4] Reisner et al.[5] reviewed the literature and found only 12 cases in children meeting the criteria of (1) macrocytic anemia with megaloblastic bone marrow, (2) exclusion of other causes of megaloblastic hematopoiesis, and (3) necessity for continued specific therapy to prevent relapse; they reported four additional cases. It is of interest that of these 16 cases, eight lacked intrinsic factor although free hydrochloric acid was present in the gastric juice.

In no instance to our knowledge has idiopathic hypoparathyroidism been reported coexistent with pernicious anemia. The present paper describes such a case.

Case Report

The patient was first admitted to St. Luke's Hospital in April, 1946, at the age of seven years. Her birth record was not remarkable and her infancy and childhood compared favorably in all respects to her only sibling. There was no known familial history of metabolic or hematopoietic disorders. Her parents vaguely described two brief episodes, one year and six months before admission, of recurrent pain and stiffness in the legs which received no medical attention. Two weeks before admission she had a "severe cold" without fever but went to school, and two days before admission she complained of not feeling well. The following morning she was kept in bed because her feet hurt. On the day of admission, one-half hour after being active in bed and eating breakfast, she was found unresponsive, with her legs stiff, and was brought to the hospital. She had a convulsion shortly after admission; pedal spasm and a strongly positive Chvostek's sign were observed on examination immediately thereafter. The serum calcium was 5.2 mg. per 100 ml.; serum phos-

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phorus, 8.2 mg. per 100 ml.; and alkaline phosphatase, 6.3 Bodansky units. The hemoglobin was recorded as 8.9 gm. per 100 ml., and the erythrocytes numbered 3,300,000 per mm.^{3} on admission. On the third hospital day the hemoglobin had risen to 12.3 gm. and the erythrocytes to 4,000,000, without specific therapy. The blood remained at these levels for the rest of her stay in the hospital. No further studies of her hematopoietic function were done at that time. Roentgenographic studies of the long bones, skull, chest and kidneys by excretory pyelogram were all normal. She showed a poor response to a course of parathyroid extract totaling 660 units in 22 days. During this time calcium administration had been limited to 1.0 gm. of calcium chloride orally twice and 1.0 gm. of calcium gluconate intravenously on three occasions. She was thought to have idiopathic hypoparathyroidism, and was started on daily doses of 10 minims of dihydrotachysterol (A. T. 10) and 15 minims of viosterol and 1.0 gm. of calcium chloride four times a day. By the thirty-third hospital day her serum calcium had risen to 8.5 mg. per 100 ml. and she was discharged to the Convalescent Hospital. There she did well, but before her discharge two months later all medications were discontinued.

During the next four years the patient was followed in the pediatric clinic. Three months after discharge from Convalescent Hospital the clinic laboratory reported the serum calcium to be 7.0 mg. per 100 ml. and the phosphorus 9.3 mg. per 100 ml. When she was next seen, in April, 1947, oral calcium gluconate, 0.3 gm. three times a day, was started. Dihydrotachysterol was not resumed until July and was continued only until October, at which time the serum calcium was 11.1 mg. per 100 ml. and the phosphorus 7.4 mg. per 100 ml. She was asymptomatic, and treatment was limited to viosterol and one quart of milk a day until October, 1949, when the serum calcium had fallen to 6.9 mg. per 100 ml. and the phosphorus was up to 9.1 mg. per 100 ml. Following the resumption of dihydrotachysterol, her serum calcium increased over the next year to 11.0 mg. per 100 ml. in October, 1950. However, she had experienced episodes of vomiting for several months, and was re-admitted to the hospital in November, 1950, at the age of 12.

On her *second hospital admission* the physical examination was unremarkable except for a smooth red tongue and lenticular opacities seen by slit lamp only. The blood contained 10.5 mg. of hemoglobin per 100 ml., 2,640,000 erythrocytes per mm.^{3} and 6,400 white blood cells per mm.^{3} with a normal differential count. The reticulocyte count was 1.6%. The bone marrow examination revealed megaloblastic hyperplasia. Two gastric analyses demonstrated no free acid following histamine.

She was considered to have pernicious anemia and was discharged after one week to have ambulatory therapy in the clinic. The serum calcium of 11.0 mg. per 100 ml. and the phosphorus of 4.8 mg.% indicated that her hypocalcemia was adequately controlled, and because of her poor response to parathyroid extract four years previously and a suggestion of short neck and moon face she was thought during this admission to have pseudohypoparathyroidism.

In the pediatric clinic she failed to respond to vitamin B_{12} by mouth, but after the addition of 8 c.c. of Ventriculin * twice daily the hemoglobin level rose from 10.5 to 12.2 gm. and the erythrocytes from 2,750,000 to 3,280,000 per mm.^{3} in one week. A reticulocyte count after one week of this therapy showed a rise from 0.5% to 3.2%. Thereafter her blood count reached normal levels and was maintained during the following year with two tablets of Dodex forte † daily at 15.0 gm. of hemoglobin per 100 ml. and 5,200,000 erythrocytes per mm.^{3} During the corresponding period of 1951, however, the serum calcium declined, ranging between

* Ventriculin (Parke-Davis): oral preparation of desiccated hog stomach; 15 c.c. equal ¼ U.S.P. antianemic unit.

† Dodex forte (Organon): contains vitamin B_{12}, 5 mcg, activated for oral administration by 500 mg. of natural pyloric substance plus folic acid, 1 mg.

6.1 and 8.8 mg. per 100 ml., and the serum phosphorus increased, ranging between 6.5 and 7.7 mg. per 100 ml., in spite of a daily regimen of 10 minims of dihydrotachysterol, 1.0 gm. of calcium gluconate and one pint of milk. She was also followed in the ophthalmology clinic, where her lenticular opacities showed no progression.

In April, 1952, about six months after an uneventful menarche, she was transferred to the hematology clinic, where she was treated with bimonthly injections of 30 mcg. of vitamin B_{12}, as well as 15 minims of dihydrotachysterol and 1.0 gm. of calcium gluconate daily by mouth. In spite of her sense of well being and normal physical findings, her serum calcium and phosphorus levels were 6.0 and 11.7 mg. per 100 ml., respectively. With increasing doses of dihydrotachysterol (to 30 minims daily) these levels were corrected to normal limits in the succeeding eight months. Meanwhile, because of skepticism regarding the diagnosis of pernicious anemia in one so young, vitamin B_{12} was discontinued. In January, 1953, 10.8 gm. of hemoglobin per 100 ml. and 3,550,000 erythrocytes per $mm.^3$ were recorded. For three months, however, she had no complaints, until in May, 1953, she came to the clinic after three weeks of lethargy, nausea and morning vomiting. She appeared to be in marked hematologic relapse and was admitted to the hospital for further study and treatment.

Physical Examination: The patient appeared to be a well developed and well nourished, somewhat small girl of almost 15 years, markedly pale but in no distress. The rectal temperature was 99.4° F. The skin was clear. The sclerae were subicteric. Slit lamp examination confirmed the presence of lenticular spoke opacities unchanged from prior admissions. The tongue was slightly smooth and pink. The lungs were clear and resonant throughout. The heart was not enlarged, but a soft blowing precordial systolic murmur was heard, loudest in the third left interspace. The pulse was 92, with normal sinus rhythm, and the blood pressure was 90/10 mm. of Hg, with the second sound changing at 55. The spleen tip could be felt at the costal margin. The extremities were unremarkable. The neurologic examination, including vibratory and position sense, was normal. No Chvostek, Trousseau or carpopedal spasm was noted.

Laboratory Data: On admission the blood contained 6.9 gm. of hemoglobin per 100 ml.; 2,260,000 erythrocytes per mm^3., and 6,600 white blood cells per mm^3., with 75% neutrophils, including 2 stab cells, 18% lymphocytes, 2% monocytes and 5% eosinophils. Slight hyperchromia and poikilocytosis and moderate anisocytosis with a tendency to macrocytosis were noted in the smear. Hematocrit was 20, and the mean cell volume was 100 $c\mu$. Reticulocytes numbered 1.2%. The sedimentation rate was 46 mm. (Westergren), corrected to 6 mm. in one hour. The serum bilirubin was 2.5 mg. per 100 ml. A gastric analysis showed histamine resistant achlorhydria with 12 units of total acid. The bone marrow was markedly megaloblastic and contained many giant metamyelocytes.

The serum calcium was 9.1 mg. per 100 ml.; the serum phosphorus, 5.1 mg. per 100 ml., and alkaline phosphatase, 2.9 Bodansky units. The blood urea nitrogen of 19.5 mg. per 100 ml. subsequently fell to 11 mg. and 8 mg. during her admission. The total plasma protein was 7.0 gm. per 100 ml., including 5.0 gm. of albumin and 2.0 gm. of globulin; the cholesterol, prothrombin and serologic determinations were all within normal limits. The urinalysis was normal, and phenolsulfonphthalein excretion was over 70% in two hours. The 24 hour stool fat content was 14% of total dry weight. The oral glucose tolerance curve following the administration of 100 gm. of glucose rose from a fasting level of 86 mg. per 100 ml. to 148, 154, 111 and 103 mg. per 100 ml., respectively, in one, two, three and four hours. The duodenal contents had a pH of 8.0 and contained 3.3 units of trypsin and 40 units of amylopsin.

Roentgenographic contrast studies of the entire gastrointestinal tract, including

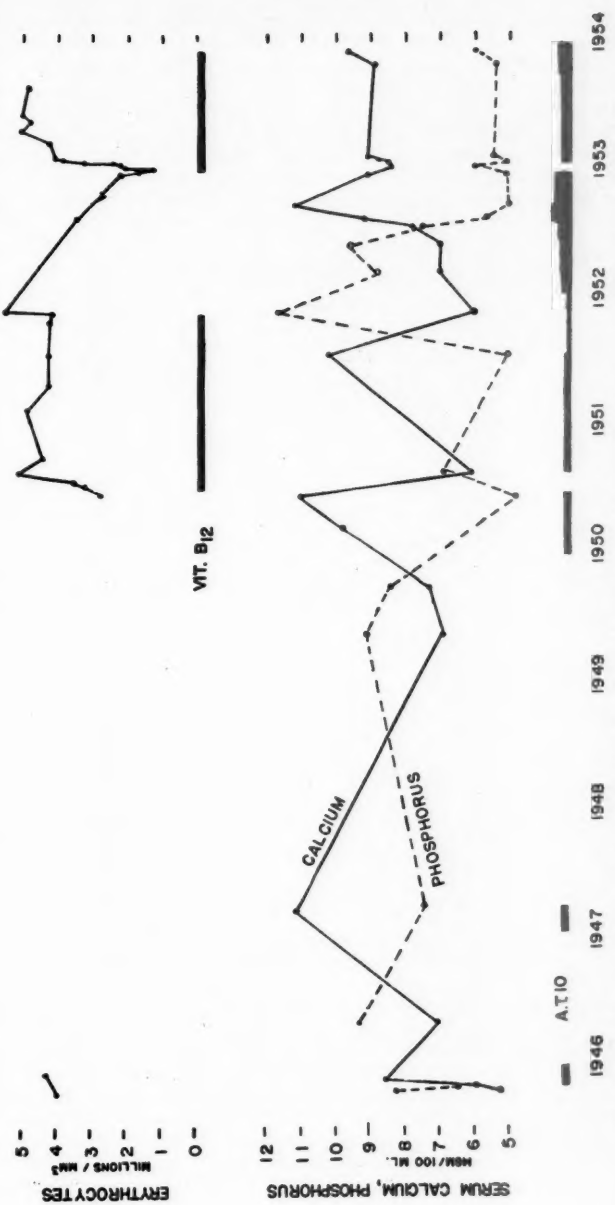

FIG. 1. Erythrocyte, serum calcium and phosphorus levels, with vitamin B_{12} and dihydrotachysterol therapy, 1946–1954.

the small intestine, were normal, as were roentgenograms of the chest, arms, hands and wrists, which showed normal metacarpal development. Slightly increased bone density was demonstrated in the x-rays of the pelvis. Stereograms of the skull showed widespread faint linear and punctate calcifications in the general location of the basal ganglia. X-rays of the teeth showed only equivocal blunting of several root apices. The electrocardiogram was normal.

Hospital Course: During the patient's first week in the hospital she appeared somewhat listless, had a poor appetite, and vomited on several occasions. To obtain a definitive diagnosis it was decided, in spite of the fairly severe megaloblastic anemia,

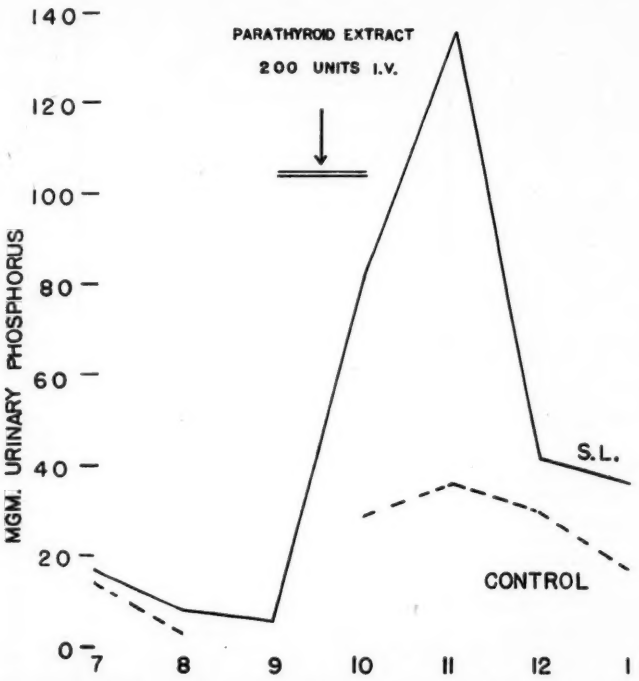

FIG. 2. Ellsworth-Howard test. Overnight urine specimens at 6 a.m. were discarded. Control patient's 9 o'clock specimen was incomplete.

to withhold all treatment, including dihydrotachysterol, to permit relapse of the well documented hypocalcemia, at the time in remission. By the twenty-fifth hospital day, when the serum calcium was 8.4 mg. per 100 ml. and phosphorus 6.0 mg. per 100 ml., she developed a positive Chvostek's sign without other subjective signs of distress. To measure the end organ response to parathyroid hormone an Ellsworth-Howard test [6] was done in the first week of her hospital stay. This showed only 45 mg. of urine phosphorus in the first hour following the intravenous injection of 200 units of parathyroid hormone. Following the correction of her anemia, the Ellsworth-Howard test was repeated after a six day period of measured calcium and

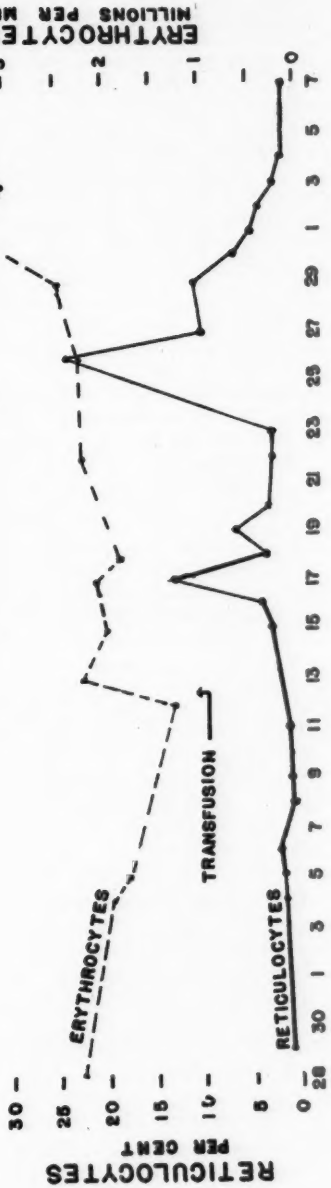

FIG. 3. Reticulocyte and erythrocyte levels before and after addition of intrinsic factor to daily oral vitamin B_{12}.

phosphorus in the diet. Following the administration of 2 c.c. of biologically potent parathyroid hormone * in 100 c.c. of isotonic saline by intravenous drip over a one hour period, the urine phosphorus in the first hour rose to 135.2 mg., compared to a rise to only 36.0 mg. in a normal control subject (figure 2). This was interpreted as diagnostic of idiopathic hypoparathyroidism.

A diagnostic trial of daily oral doses of 5 mcg. of vitamin B_{12} produced no reticulocyte response in eight days. Meanwhile the hemoglobin fell to 5.1 gm. per 100 ml. and the erythrocytes to 1,280,000 per mm.^{3} Following a transfusion of 250 c.c. of packed washed erythrocytes, which raised the hemoglobin to 7.8 gm. per 100 ml. and the erythrocytes to 2,230,000 per mm.^{3}, the patient was started on a daily oral dose of 1.25 mcg. of vitamin B_{12}, together with 2 mg. of an intrinsic factor concentrate of animal origin.† An initial peak of 13.3% reticulocytes was reached after five days of this dose, which was then increased to 5 mcg. of B_{12} a day, with 8 mg. of intrinsic factor concentrate; a second reticulocyte peak of 23.7% occurred after eight days of the higher dosage. Thereafter she was given 50 mcg. of B_{12} by the intramuscular route twice weekly, and her anemia continued to show steady improvement (figure 3).

Following the resumption of 15 minims of dihydrotachysterol and 3 mg. of calcium gluconate daily she became asymptomatic, although still demonstrating a positive Chvostek's sign, and she was discharged on the thirty-ninth hospital day to be followed in the out-patient department. Ten days later the following determinations were noted: serum calcium, 9.1 mg. per 100 ml.; serum phosphorus, 5.5 mg. per 100 ml.; hemoglobin, 12.2 gm. per 100 ml.; erythrocytes, 4,080,000 per mm.^{3}

Since July, 1953, the patient has been maintained in the clinic on a regimen consisting of 20 minims of dihydrotachysterol daily; calcium gluconate, 2 gm. three times a day; 20 minims of viosterol daily, and intramuscular vitamin B_{12}, 30 mcg. monthly. The peripheral blood counts have been entirely within normal limits, and the serum calcium and phosphorus are adequately controlled on the above regimen.

Discussion

The unlikelihood of two uncommon conditions coexisting in the same patient led to initial consideration of the possibility that the hypocalcemia and the macrocytic anemia might have a common etiology in some defect of intestinal absorption. Macrocytic anemias are occasionally encountered in infants with celiac disease, as is tetany. In adults with the sprue syndrome, megaloblastic anemia is common but tetany is rare. In this patient there was no history of steatorrhea, and arguing clearly against an adult sprue syndrome was the reciprocal hyperphosphatemia. Moreover the normal stool fat content and duodenal enzyme distribution, normal oral glucose tolerance curve, and normal roentgenographic studies of the upper gastrointestinal tract, including the small intestine, added to discount any sprue syndrome in the differential diagnosis. Sprue was further ruled out by the reticulocyte response to oral vitamin B_{12} when intrinsic factor was added, a response which served to establish the diagnosis of pernicious anemia.

An earlier impression of pseudohypoparathyroidism was dispelled by the Ellsworth-Howard test,[6] which showed a marked increase in urinary phosphorus excretion typical of idiopathic hypoparathyroidism rather than absence of any such response, as would be expected in pseudohypoparathyroidism, where

* Parathyroid hormone of proved potency was generously supplied by Dr. Fuller Albright, Massachusetts General Hospital, Boston, Massachusetts.

† This preparation was obtained from Dr. Thomas B. Jukes, Lederle Laboratories Division, American Cyanamid Corporation, Pearl River, N. Y.

there is absence of end organ response to normal amounts of the circulating hormone. Our initial experience with the first of two such tests emphasizes the importance of obtaining parathyroid hormone of proved potency in conducting the Ellsworth-Howard test. X-ray studies also failed to show the characteristic metacarpal shortening associated with pseudohypoparathyroidism; nor was there any retarding of the development of the secondary sex characteristics in this patient, such as is found in the pseudohypoparathyroid syndrome.[7]

In a consideration of the etiology of these two diseases, neither idiopathic hypoparathyroidism nor pernicious anemia appears to implicate the other. It can be speculated whether calcium salts or dihydrotachysterol used in the treatment of the parathyroid deficiency, the first of the two diseases to be recognized, could have in any way interfered with elaboration of intrinsic factor by the gastric mucosa. However, in the third admission this girl had persistent achlorhydria and absence of intrinsic factor, as shown by the failure of reticulocyte response to oral vitamin B_{12} alone when all medications for the hypoparathyroidism had been deliberately withheld for 17 days.

Peripheral blood counts on the one hand, and serum calcium-phosphorus levels on the other hand (figure 1), fail to show any pattern of coincidence or reciprocal relationship. In April, 1946, the hemoglobin was 12.4 gm. per 100 ml. when calcium determinations were quite low. In November, 1950, when the calcium was high (at a level of 11.0 mg. per 100 ml.), hemoglobin was depressed to 11.0 gm. per 100 ml. Two months later, when anti-pernicious anemia therapy had brought the hemoglobin up to normal, the serum calcium had plummeted to 6.1 mg.%. One year later both were satisfactory, with the hemoglobin 13.1 gm. per 100 ml. and serum calcium 10.2 mg. per 100 ml. It is apparent that the relapses of hypocalcemia and anemia are attributable to the withholding of dihydrotachysterol and vitamin B_{12}, respectively.

Vomiting in this case is adequately explained by the pernicious anemia,[8] and was present only when the pernicious anemia was in relapse. Nausea and vomiting occurred in only one case in a tabulation of symptoms in 50 cases of idiopathic hypoparathyroidism.[1] Somewhat larger daily doses of dihydrotachysterol prior to the last admission might be incriminated as causing gastric irritation, but this drug had not offended at other times, nor has it since the patient's recent discharge.

Summary

A case is reported in which severe hypocalcemia with associated hyperphosphatemia was first discovered when the patient at the age of seven had a tetanic convulsion followed by coma. At the age of 12 she developed a macrocytic anemia characterized by megaloblastic bone marrow and histamine-fast achlorhydria. Her clinical course between admissions has reflected the adequacy of therapy for conditions diagnosed at the age of 14 as idiopathic hypoparathyroidism with coexistent pernicious anemia.

Summario in Interlingua

Nos crede que isto es le prime reporto de un caso de coexistentia de hypoparathyroidismo idiopathic e anemia perniciose.

Un revista del litteratura, publicate per Steinberg e Waldron in 1952, compilava 52 casos de hypoparathyroidismo idiopathic; 36 de illos concerneva patientes de etates

de infra 20 annos. Reportos de perniciose anemia addisonian in juveniles es ancora plus rar. Un revista del morbo in juveniles, publicate per Reisner *et al.* in 1951, poteva listar non plus que 16 casos.

In le subjecto del presente reporto, sever hypocalcemia associate con hyperphosphatemia esseva primo discoperite al etate de 7 annos quando illa suffreva un convulsion tetanic sequite per coma. Al etate de 12 annos illa disveloppava un marcate anemia macrocytic, characterisate per megaloblastosis del medulla ossee e achlorhydria refractori a histamina. In figura 1 nos presenta un tabulation chronologic del curso del caso durante e inter tres hospitalisationes ab 1946 a 1954, exhibiente le nivellos seral de calcium e phosphoro, con therapia a vitamina B_{12} e dihydrotachysterol. Le tabulation reflecte le sufficientia del therapia pro le duo distincte conditiones que esseva definitemente diagnosticate como hypoparathyroidismo idiopathic e anemia perniciose al etate de 14 annos. Nos discute le diagnose differential e le impossibilitate de combinar le duo morbos per un sol etiologia.

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HYPOPROTHROMBINEMIA FOLLOWING THE USE OF PROPYLTHIOURACIL: CASE REPORT*

By GERALD P. MIRRER, M.D., *Douglaston, N. Y.*

THE most frequent toxic manifestations in the clinical use of propylthiouracil include drug fever, dermatitis, agranulocytosis and leukopenia.

Severe hypoprothrombinemia following propylthiouracil therapy was described by Craddock et al.[1] In their experience fresh human thrombin free serum, together with whole blood transfusions, resulted in a rapid decrease of the prothrombin time. Vitamin K parenterally failed to exert a hemostatic effect.

The following is a report of hypoprothrombinemia which occurred during propylthiouracil administration in a case whose presenting symptoms were hematuria and purpura.

* Received for publication August 23, 1954.

Case Report

The patient was a 43 year old white Italian female who had been on antithyroid medication because of hyperthyroidism since January, 1953. The cardinal manifestations of her illness at that time were an insidious onset of weight loss, tremors of the fingers, intolerance to heat, a moderately elevated basal metabolic rate and a diffusely enlarged thyroid gland. These signs and symptoms developed while her father was ill and progressed after his death. The patient was treated with Tapazol, 10 mg. three times a day in conjunction with phenobarbital. The latter medication was taken for a brief period. Within two months a euthyroid status was attained. There was a gain in weight, loss of tremors and an increased tolerance for heat. The thyroid gland remained enlarged. No bruit was audible. In October 1953, she was arbitrarily placed on propylthiouracil, and Tapazol was discontinued. Blood counts done periodically during therapy were normal. The clinical course remained unchanged except for several episodes of bronchitis in December. Sputa examinations showed streptococcus and staphylococcus. The patient responded favorably to oral aminophylline, saturated solution of potassium iodide, five drops three times a day, and Ilotycin, 200 mg. four times a day. The above medication was discontinued within three days. The thyroid gland remained palpable but was decidedly smaller. Propylthiouracil was continued with a view toward decreasing the dose and then stopping the drug.

The past history as well as the family history was noncontributory as to any bleeding tendency. There has been no menorrhagia or metrorrhagia.

On March 18, 1954, the patient was seen because of painless hematuria of one day's duration. She complained of a vague discomfort in the lower back. Interrogation disclosed intermittent bleeding from the ring finger that had been traumatized on March 10, generalized fatigue for one week, and pain in the right cheek associated with mastication. There was no antecedent upper respiratory infection or sore throat, and no chills or fever. The ingestion of medication other than propylthiouracil was denied. Because of these complaints propylthiouracil was discontinued as of this day (March 18).

Clinical examination disclosed a well developed, well nourished white female who appeared pale. Blood pressure, 120/80 mm. of Hg; weight, 113 pounds; pulse rate, 100 per minute; temperature, 99.0° F. oral. No petechiae or splinter hemorrhages were present. The mucous membranes were pale. The thyroid gland was not palpable. The lungs were clear to percussion and auscultation. The heart sounds were normal, with a regular sinus rhythm; no thrills or murmurs were noted. There was exquisite bilateral costovertebral angle tenderness. The Rumpel-Leede test was negative. Cystoscopy done one day later disclosed a normal bladder. Blood was seen streaming from both ureteral orifices. The patient was instructed to discontinue propylthiouracil and to adhere to a restricted fluid diet high in calories and low in protein. She was placed on tetracycline, 250 mg. every six hours. The urine continued to be bloody for the next six days. Laboratory data disclosed hemoglobin, 10 gm.; red blood cells, 3.3 million; adequate platelets on peripheral smear; hematocrit, 32; sedimentation rate, 36 (Wintrobe); blood urea nitrogen, 17 mg.%; total protein, 6.15 gm.; albumin, 3.18; globulin, 2.3.

On March 23 excessive uterine bleeding was noted. One area of purpura was observed on the left hypothenar eminence. The ring finger became infected. A cough productive of blood-tinged sputa developed. The patient was given one injection of penicillin and placed on oral vitamins C and K, as well as 10 mg. of vitamin K parenterally. The uterine bleeding decreased for several hours. Pain in the right parotid gland during mastication continued. The patient was hospitalized on March 25.

On the evening of admission she complained of severe low back pain associated with tightening of the hamstring muscles. The injured finger bled profusely. Another large purpuric zone developed on the proximal third of the left tibia. The liver, spleen and lymph nodes were not enlarged. Blood pressure was 110/70 mm. of Hg. Neurologic examination was within normal limits. There was a positive Lasègue's sign bilaterally. Urinalysis showed 3 plus albumin with 25 red blood cells; hemoglobin, 8.5 gm.; white blood cells, 10,000; differential, normal; reticulocytes, 6; platelets, 155,000; bleeding time, 2 minutes; coagulation time, 32 minutes (Lee-White); clot retraction, normal; prothrombin time, 29 seconds (control, 13 seconds); serum bilirubin, normal; blood fibrinogen, 1:800 (control, 1:400); cephalin flocculation, negative. Alkaline phosphatase, 2.1 Bodansky units; cholesterol, 184 mg.%; esters, 146 mg.%. A chest film was negative. Within 12 hours the hemoglobin decreased from 8.5 gm. to 7.0 gm. The patient's clinical condition appeared critical. She was treated with 5.0 c.c. of vitamin K_1 oxide intravenously, one unit of whole blood and 300 mg. of cortisone in divided doses orally. A second blood transfusion and 5.0 c.c. of vitamin K_1 oxide were administered the following day. Cortisone was continued in smaller doses over a four day period. Within 24 hours the clinical course improved dramatically. The back pain and the uterine and renal bleeding subsided. A firm clot was present on the ring finger. The pain in the parotid gland subsided. The prothrombin and clotting times were normal when tested 24 hours later. There was a gradual rise in the hemoglobin, and there have been no further episodes of purpura or renal bleeding in a three month follow-up.

Discussion

The common etiologic factors in the causation of hypoprothrombinemia include lack of vitamin K, liver damage, toxins, salicylate administration, and idiopathic hypoprothrombinemia. It seems unlikely that a lack of vitamin K played a rôle in producing hypoprothrombinemia in this case, because of an adequate dietary intake and an equivocal response to parenteral vitamin K. There were no other signs of vitamin deficiency, no jaundice and no recent ingestion of broad spectrum antibiotics. Liver function tests were within normal limits. Salicylates and toxins (coumarin compounds) were denied. Idiopathic hypoprothrombinemia is unlikely because of the patient's age and a negative family history.

In view of the severe bleeding and nerve root irritative symptoms in this case, whole blood transfusions, cortisone and vitamin K_1 oxide were used. From the above it is apparent that vitamin K did not affect the prothrombin time. Because of the severe stress reaction, cortisone was given a trial. It is postulated that whole blood transfusions provided the plasma factor (labile factor) for correcting the prothrombin time and clotting time. In view of the temporary nature of this condition a toxic reaction to propylthiouracil is suggested.

Summary

This is a case of a 43 year old white Italian female who was treated with propylthiouracil for six months because of hyperthyroidism. The presenting signs indicative of a complication were bleeding from the genitourinary tract, and purpura. The significant laboratory data disclosed hypoprothrombinemia and a prolonged clotting time. There was a dramatic salutary response to blood transfusions, vitamin K_1 oxide and cortisone.

SUMMARIO IN INTERLINGUA

Es presentate le caso de un maritate femina italian de 43 annos de etate qui esseva tractate con drogas antithyroide—i.e. Tapazol e plus tarde propylthiouracil—a causa de symptomas e signos clinic de hyperthyroidismo.

Post cinque menses del curso de propylthiouracil illa disveloppava subitaneemente non-dolorose hematuria e purpura. Isto esseva sequite per sanguination uterin, hemoptysis, e signos neurologic de incipiente involvimento del medulla spinal. Le possibilitate de un morbo focal in le vias urinari esseva excludite per cystoscopia.

Le significative datos laboratorial indicava anemia, albuminuria, hematuria microscopic, un negative test de Rumpel-Leede, normal tests del functiones hepatic, un normal conto de plachettas, un normal nivello de fibrinogeno, e prolongation del tempore de coagulation e del tempore de prothrombina. Le patiente esseva tractate con intravenose oxydo de vitamina K_1, un transfusion de sanguine, e cortisona oral. Intra 24 horas le curso clinic se ameliorava frappantemente. Le tempore de prothrombina e le tempore de coagulation retornava a valores normal. Le patiente recuperava sin incidente.

Hypoprothrombinemia idiopathic e hypoprothrombinemia attribuibile al causas usual—per exemplo absorption defective o carentia de vitamina K_1, lesion hepatic, toxinas, salicylatos, e anticoagulantes—esseva excludite o per le historia del patiente o per datos laboratorial. Iste facto insimul con le prompte responsa biologic del patiente indica in nostre opinion que reaction toxic a propylthiouracil es le plus probabile factor etiologic. Nos postula que le transfusion de sanguine integre forniva le deficiente factor plasmatic (factor labile) que esseva requirite pro corriger le tempore de prothrombina e le tempore de coagulation.

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DIFFUSE INTERSTITIAL PULMONARY FIBROSIS *

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IN 1944 Hamman and Rich [1, 2] described three cases of diffuse interstitial fibrosis of the lungs observed by them between 1931 and 1933, and an additional case seen in 1943. These cases were characterized by dyspnea, cyanosis and cor pulmonale attributable to a widespread connective tissue hyperplasia throughout the interstitial structures of the lungs. Several etiologies were considered and discarded as incompatible with the pathologic findings, and the syndrome was believed to represent an acute idiopathic entity.

In the subsequent decade it has become increasingly clear that the syndrome represents a general tissue response of the lungs. This reaction in itself proves an advantage to the organism when it is confined to a relatively small area and is instrumental in the reparative process, such as the walling off of a granuloma or the repair of an infarct, but is a distinct disadvantage when diffuse and widespread.[3]

* Received for publication June 3, 1955.
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Clinically the disease is manifest by dyspnea, which is often exertional at first but frequently increases to a resting dyspnea, and cough, which is most often nonproductive or only slightly productive. Easy fatigability and weight loss are often present, whereas cyanosis, polycythemia and cor pulmonale [4] are noted most often when the disease has become severe. Physical findings are often minimal,[4, 5] and may be limited to occasional coarse râles and rhonchi. Clubbing of the fingers is an inconstant finding. X-rays reveal a bilateral diffuse mottling through the lung fields.

Two characteristic aspects of the clinical course are its very insidious onset and the irremediable progression of pulmonary and cardiac impairment. The former may explain the acute appearance of some cases, which very likely represent the end stages of a prolonged and gradual subclinical exhaustion of respiratory reserve.[5] Support for this thesis is noted even in the first case reported by Hamman and Rich, which demonstrated on postmortem examination much old diffuse scarring but little recent active connective tissue formation. Survival after the onset of symptoms may be a matter of weeks or of several years, with increasing disability.

The pathologic picture of pulmonary fibrosis is that of firm and heavy lungs which are granular and fibrous on sectioning. Hypertrophy and dilatation of the right side of the heart may be noted. Microscopic examination reveals a diffuse collagenous hyperplasia in the interstitial peribronchial and perivascular areas. The alveolar septa are widened by excessive fibroblastic activity, capillaries are dilated, and the alveolar epithelial cells may show proliferation in some regions and necrosis elsewhere. The presence of abnormal numbers of eosinophils in the interstitial tissues is an inconstant finding, as is the hyaline membrane lining the alveoli. The latter has been attributed to protein-containing fluid which had previously entered the alveoli. Leukocytic infiltration is notably lacking, as are stainable bacteria, fungi and inclusion bodies. Arterioles often show a subintimal proliferation.

It is worth repeating that fibrosis of the lung is a rather nonspecific and general tissue reaction of that organ. With this consideration in mind, it is obvious that the etiologic agents which have been implicated are numerous. Among those recognized and relatively well understood are: tuberculosis, silicosis and several other pneumoconioses, mycotic infections, and organizing pneumonias. Less well understood entities such as periarteritis nodosa, disseminated lupus erythematosus and scleroderma also may demonstrate pulmonary fibrosis.[3]

There remains, however, a group of patients in whom no etiologic agents can be demonstrated by current clinical or pathologic technics, and the elaboration of factors contributing to idiopathic fibrosis is of prime importance to any basic understanding of the disease. Few of these factors have been described, and little attention has been paid to possible genetic or constitutional predisposition.

Because of the infrequency with which idiopathic pulmonary fibrosis has been noted in siblings, and because of the close clinical and pathologic similarity noted between the following two cases, it was thought of interest to report them.

Case Reports

Case 1. The patient was a 52 year old white male bartender who had been healthy most of his life but did recall three brief episodes between 1933 and 1945 of

left chest pain unaccompanied by any other notable symptoms and diagnosed as pleurisy. In 1942 the patient was rejected for Army service because of an abnormal chest x-ray diagnosed as a "slight case of tuberculosis." No further examination or treatment was instituted at that time. The patient remained symptomatically well until 1948, when he noted a slight hacking cough, mostly on arising, productive of small amounts of a thin white sputum.

Dyspnea on exertion developed in 1953 and subsequently progressed, as did the cough. At no time was there hemoptysis, fever or night sweats. In June, 1953, he consulted a physician and again an abnormal chest x-ray was noted. Sputum examined for acid-fast bacilli was negative. Therapy with streptomycin, isonicotinic acid hydrazide and Terramycin was instituted, but the symptoms continued to get worse and were accompanied by weight loss and easy fatigability, requiring him to give up employment.

On August 4, 1953, the patient was admitted to the University of Chicago Clinics, giving the above history and noting that his mother had died of "bronchopneumonia," and that his brother died at age 38 of pulmonary fibrosis. (Originally the patient had had seven siblings; one died of a cerebrovascular accident, one in infancy, and one of pulmonary fibrosis. Two brothers and two sisters were living and well.)

Physical examination revealed a small, emaciated white male who appeared dyspneic and cyanotic. Blood pressure was 90/60 mm. of Hg; pulse, 128; respiration, 48. Eyes, ears, nose and throat were negative. The chest was hyperresonant to percussion, and diaphragmatic movements were diminished. Coarse râles in both bases and scattered inspiratory rhonchi could be heard. Examination of the abdomen, genitalia, rectum, extremities and central nervous system was negative.

Tuberculin skin test was negative at 1:10,000 O.T. and positive at 1:1,000. No acid-fast bacilli were found in the sputum by direct smear or by culture. Pseudomonas species was noted on throat culture. Serum chloride was 102.6 mM/L; CO_2, 28.1 mM/L. Total protein was 6.8 gm.%; albumin, 3.1 gm.%; globulin, 3.7 gm.%. Blood urea nitrogen was 13.5; Kahn, negative; white blood cells, 10,600; hemoglobin, 13.0 gm.; red blood cells, 4.0 million; hematocrit, 40; sedimentation rate, 50, corrected to 36; differential: neutrophils, 69; large lymphocytes, 3; small lymphocytes, 26; monocytes, 3; eosinophils, 0; basophils, 0. Urinalysis was negative; stools were negative to benzidine test for occult blood.

Chest x-ray (figure 1) showed multiple bilateral tiny densities, often following the vascular pattern and sometimes coalescing into patchy infiltrates. X-rays of the right hand and right foot failed to show either pulmonary osteoarthropathy or the bone lesions of sarcoidosis.

Electrocardiogram demonstrated a sinus tachycardia with a low T_I and $T_{V/5}$. The vital capacity was 18% of predicted normal. Maximal breathing capacity was also quite reduced.

Therapy with ACTH (60 units daily), antibiotics (penicillin and Terramycin), potassium iodide, theophylline and oxygen failed to have a significant effect on the course of the disease, though the patient felt somewhat better symptomatically. Through the period of progressive clinical deterioration neither a secondary polycythemia nor physical signs of cor pulmonale was noted. On April 24, 1954, the patient died after having complained some hours previously of a pain in his chest.

Significant findings at autopsy were a hypertrophy of the right ventricle measuring 5 to 8 mm. in thickness, and uniformly firm and fibrous lungs which did not collapse when the chest was opened. "Over the entire surface of both lungs the pleura is smooth, glistening and free of adhesions. It is covered with multiple nodules and blebs which measure from 2 to 12 mm. in diameter and consist of elevated lung tissue which is moist and reddish brown. Both lungs cut with greatly increased resistance and the cut section presents much the same appearance as the external

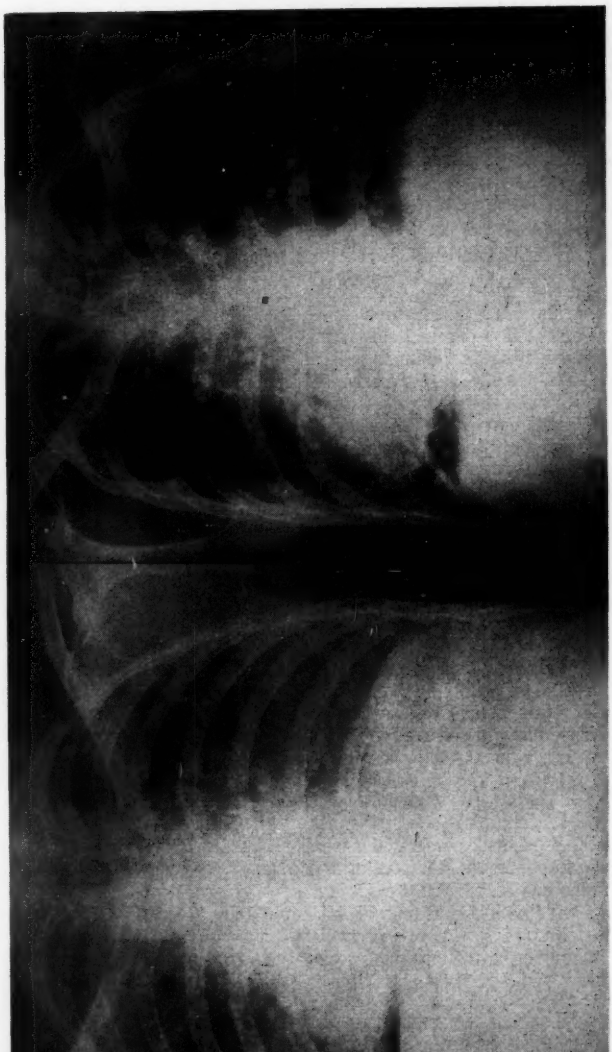

FIG. 1. Generalized patchy infiltrates characteristic of pulmonary fibrosis obscure the lung fields of case 1 (right) and case 2 (left).

surface with uniform fibrosis throughout with multiple fibrous septa forming nodules ranging from a few millimeters in diameter to approximately 1 cm. in diameter. A few of these nodules contain calcified material. The bronchi appear dilated and their walls somewhat stiffened. The blood vessels appear normal. The calcified material in the nodules appears to be loose in cavities and on section the calculi fall from their nodules easily.

"The peribronchial and hilar lymph nodes are enlarged, measuring from 1 by 1 by 3 cm. to a cluster measuring 3 by 2 by 3 cm. These enlarged nodes are anthracotic with scattered fibrotic nodules."

Both adrenals showed uniform hyperplasia, the right weighing 12.5 gm. and the left 14.5 gm.

The remainder of the autopsy was normal except for some sigmoid diverticula. Microscopic examination showed the lungs "diffusely infiltrated by a network of relatively acellular fibrous tissue. The amount of collagen varied from place to place with some areas having large quantities of hyalinized connective tissue (figure 2). Areas of proliferating young fibroblasts in thickened alveolar walls were present at the edges of the remaining nests of parenchymal cells. The alveoli were decreased in number and those remaining were dilated. There was marked metaplasia of the alveolar lining cells. Many alveoli contained edema fluid and large numbers of polynuclear leukocytes. Small islands of bone were present. No giant cells were found. Some pulmonary vessels had marked intimal and sub-intimal thickening." Micro-incineration of sections of lung tissue failed to reveal abnormal amounts of noncombustible material which might have caused a pneumoconiosis.

A moderate lymphangitis was noted throughout the peribronchial lymph nodes.

The heart showed uniform hypertrophy of myocardial fibers, and the adrenals showed a hypertrophy and prominence of the zona fasciculata. The bone marrow was hypocellular with active erythropoiesis.

Case 2. The patient was a 38 year old white male (brother of case 1), presumably in good health until about 1944, when he noted dyspnea, cough and weight loss, for which he consulted several private physicians. Several diagnoses were suggested but therapy was generally unavailing. Due to progression of the patient's symptoms he presented himself at the Veterans Administration Hospital in New Orleans, Louisiana. At that time his cough was productive of 6 to 7 ounces of thick mucoid sputum daily. He had lost 25 pounds and was able to walk only 25 yards without severe dyspnea.

The only significant item of past history noted was that of employment in an asbestos factory 12 years prior to admission.

While in the hospital the patient was carefully and extensively investigated. Numerous sputum cultures were negative for both acid-fast bacilli and fungi. Sputum was also negative for malignant cells. Tuberculin was positive on a second strength test; skin tests with histoplasmin and coccidioidin were negative. Chest x-rays (figure 1) showed a "generalized progressive interstitial infiltration," and electrocardiogram demonstrated right ventricular strain. Scalene nodes were removed and found negative by microscopic examination and on culture. Subsequently a thoracotomy was performed and the left upper lobe of the lung was biopsied. Histologically the biopsy showed "chronic interstitial pneumonitis with much fibrosis."

Due to his symptomatic improvement during hospitalization the patient chose to leave the hospital, though therapy with ACTH and cortisone was proposed. He was discharged on May 13, 1952. Until September of that year the patient noted no progression of a symptom, but then four months prior to his second admission an exacerbation occurred.

Physical examination revealed a severely dyspneic and cyanotic white male, with coarse and fine râles audible throughout both lung fields. P_2 was louder than

FIG. 2. Diffuse connective tissue proliferation obliterates most of the alveoli. Thin collagenous fibers and active fibroblasts are seen adjacent to areas of thick hyalinized connective tissue. A clump of lymphoid or round cells is present. Epithelioid and giant cells are notably lacking.

A_2. Clubbing of fingers and toes was present. The remainder of the physical examination was negative. Many laboratory procedures already reported were repeated and were negative, including a normal serum CO_2. An electrocardiogram now showed right ventricular strain plus myocardial ischemia. *Staphylococcus aureus* and beta streptococci were found in the sputum. Initial blood counts were normal except for a leukocytosis of 11,900, which subsequently rose to 17,200, with 92% polys.

In spite of a therapeutic program which included oxygen, penicillin, ortoxin, potassium iodide and aminophylline, the patient still remained dyspneic in the oxygen tent and became cyanotic on slight exertion. On intravenous ACTH the patient's appetite and weight improved, as did his morale. After four weeks of therapy an attempt was made to decrease the ACTH and gradually substitute cortisone for it so that he might be on oral medication. During the period of gradual ACTH withdrawal the patient noted an acute, severe exacerbation, with marked dyspnea and a very productive cough. In spite of a prompt return to the level of ACTH which had previously allayed symptoms, plus cortisone and nebulized Alevaire (a detergent employed to liquefy tenacious sputum) the patient became comatose and died on March 6, 1953.

Autopsy findings were essentially normal except for the organs to be described below:

Lungs: "On opening the pleural cavities, there are no adhesions or fluid and the lungs are immediately noteworthy for their appearance is very similar to a cirrhotic liver. The surfaces are studded with small blebs approximately 2 to 3 mm. in diameter and the lungs present a firm, tough consistency to palpation, although there is some sensation of crepitation. The combined weight of the lungs is 1,400 gm. The right lung is composed of the normal 3 lobes with the visceral pleura presenting the previously noted studded appearance from the blebs. The left lung is composed of the normal 2 lobes with some scarring over the area of previous biopsy on the upper lobe. On sectioning of both lungs, the studded pinkish gray appearance is noted to extend throughout the body of the lungs. The entire lung parenchyma appears to be a mass of these emphysematous blebs. On opening the bronchi there is noted a small amount of moderately tenacious mucus."

Heart: "The heart appears grossly enlarged to approximately twice normal size. The weight of the heart is 320 gm. The right heart is enlarged."

Right Auricle: "The right auricle is somewhat enlarged in size but of normal shape. The endocardium is smooth and glistening and red-tan. The tricuspid valves appear to be of normal size and configuration measuring 12.0 cm. The right ventricle appears to be approximately double size with the wall of the ventricle being twice normal thickness measuring up to 1.5 cm. The pulmonary valve is of normal size and configuration with the cusps being thin and delicate. The left auricle is questionably enlarged with the endocardium being smooth and glistening and red-tan. The mitral valve is of normal circumference. The left ventricle is enlarged almost twice its normal size with the myocardium also being approximately twice its normal thickness. The coronary ostia are patent with no evidence of encroachment by atherosclerotic plaques. Sections through various levels of the heart reveal no fibrosis or scarring of the myocardium."

Adrenals: "Both adrenals are questionably enlarged. At least, they are at the upper limits of normal in size. The cortex is golden yellow and lobulated. There is grossly possibly some thickening of the cortex. The medullary portion is light gray and shows nothing remarkable."

Splenomegaly and pulmonary lymphadenopathy were also noted, along with testicular atrophy.

fibroblasts are seen adjacent to areas of thick hyalinized connective tissue. A clump of lymphoid or round cells is present. Epithelioid and giant cells are notably lacking.

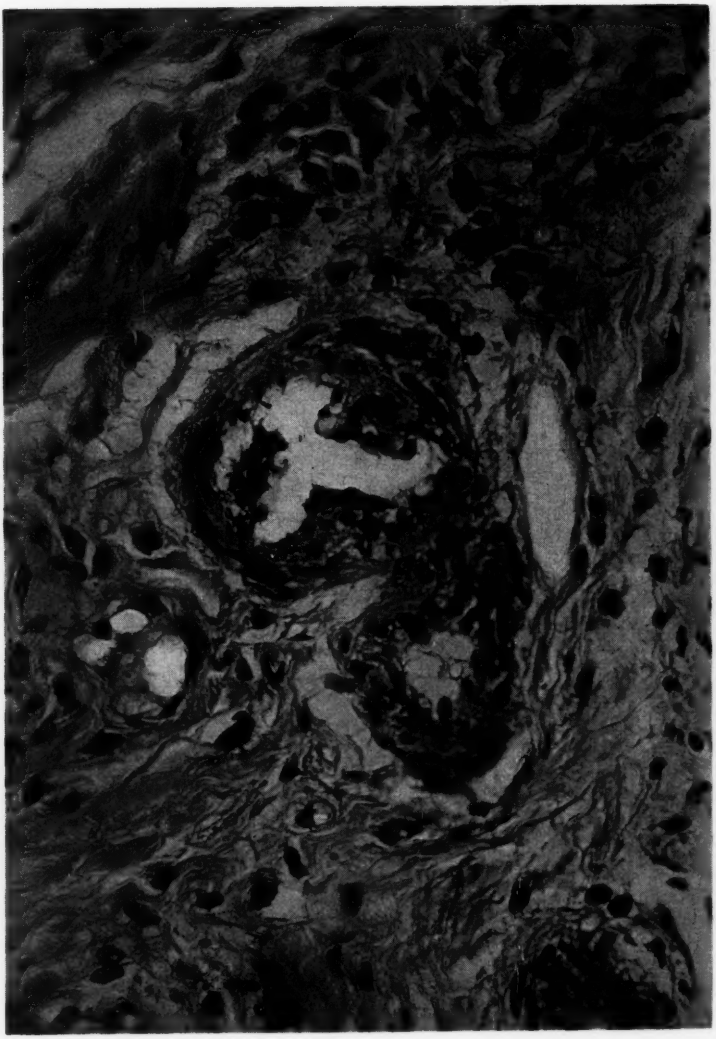

FIG. 3. Alveoli are replaced by connective tissue which, in some places (upper right), is well organized into thick bands. Subintimal proliferation is seen in the two large blood vessels.

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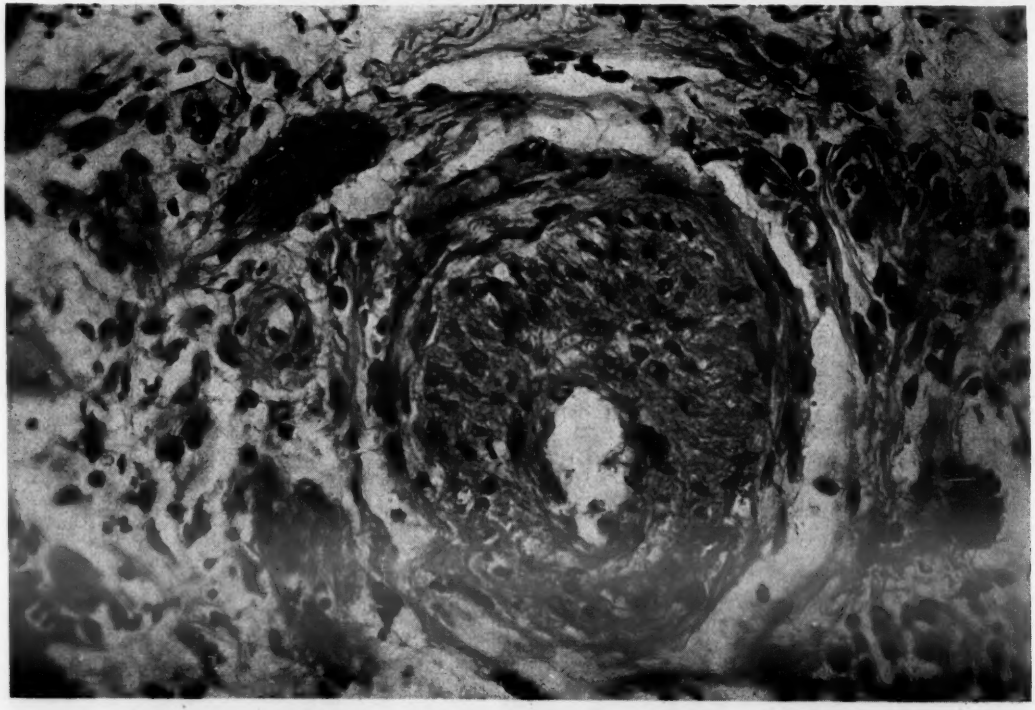

FIG. 4. Marked intimal and subintimal proliferation in a pulmonary arteriole with a severely narrowed lumen.

On microscopic examination of the lungs the alveolar walls were greatly thickened by fibrous tissue, greatly reducing the size and number of alveolar spaces (figure 3). The individual alveoli were larger than usual. The alveoli were lined by a prominent simple squamous epithelium or a columnar epithelium. Some of the alveoli were empty, but others contained some blue-staining material and others contained red blood cells, with macrophages containing brownish granular material. The thickened alveolar walls contained a proliferation of capillaries which appeared to be engorged with blood. The larger vessels had thickened walls and narrowed lumens (figure 4). There was nothing suggestive of epithelioid cells or giant cells.

Discussion

Of approximately 30 cases of idiopathic pulmonary fibrosis thus far described, it is remarkable that at least two sets of siblings and perhaps three have been found with the disease. Although pulmonary fibrosis is no longer considered a rare disease, it is relatively uncommon, and the chances of sporadic cases developing at random in the same family seem remote. Familial incidence of a disease may be related to either environmental factors or a similar genetic background. That the former are not operative to the exclusion of the latter is evidenced by the report of pulmonary fibrosis occurring in identical twin sisters who were geographically separated for at least 25 years prior to the onset of symptoms.[5, 6]

Further evidence against environmental factors is the absence of any reports of the disease in marital partners, who would be expected to share a common environment but possess a dissimilar heredity.

In the most general terms, it is of course fruitless to attempt a separation of environment from genetic predisposition, since both are operative to some extent in the formation of every biologic character. However, from a more circumscribed viewpoint it is of great importance to recognize that idiopathic pulmonary fibrosis may be akin to that group of diseases which, like diabetes mellitus and tuberculosis, have one or several precipitating etiologic factors operative on a background of inherited predisposition. The importance of this concept to experimental study of the production of disseminated pulmonary fibrosis is obvious.

Pulmonary fibrosis has been found in association with the so-called "collagen diseases," [7, 8] and in some cases it has been almost impossible to discern significant differences between the pulmonary pathology of idiopathic fibrosis and the pulmonary manifestation of one of the collagen diseases. A marked similarity was noted between the histology of case 1 and the appearance of scleroderma of the lung. The question may justly be raised as to whether the Hamman-Rich syndrome represents localized scleroderma, but against this point of view is the generalized nature of the collagen diseases, with their multiple system involvement.

One further facet of pulmonary fibrosis deserves consideration. The Hamman-Rich syndrome was first described as an acute disease, but later reports have indicated that the onset and progress may be insidious, and may occur over the course of many months or even many years.[6, 10] It is not inconceivable that the final and preterminal decompensation appears acute and alarming. This view of pulmonary fibrosis may shed light on recent reports of the disastrous effects of diminishing the dose of ACTH or cortisone, once an appropriate course of ther-

apy has been initiated. The contention that reduction in exogenous ACTH or cortisone may precede a fatal exacerbation is sufficiently well documented to warrant great care. However, this circumstance may also be interpreted as the coincidence of a dosage change with an inevitably fatal outcome, steroid therapy being currently reserved for this serious end stage of pulmonary fibrosis. In this respect, a comparison of the cases cited is instructive.

In case 1 a constant dose of ACTH (60 units) was maintained without diminution for five weeks prior to the patient's death, with mild symptomatic improvement during that time but without persistent alteration of the course of the disease. After the drop in dosage of ACTH in case 2, even the quite prompt restoration of much more than the original dose of ACTH plus cortisone failed to halt the patient's deterioration.

A comparison of longevity of the two brothers from a roughly analogous stage of their illness (i.e., when they were both so incapacitated as to require hospitalization, and when oxygen therapy became necessary to combat cyanosis and a resting dyspnea) demonstrates that it was almost identical, though one was treated with an unchanging dose of ACTH and the other with a diminished dose just prior to his death. Future comparisons of this nature may shed light on the optimal dosage program of ACTH and cortisone.

Summary

1. The history and clinical course of diffuse interstitial pulmonary fibrosis are discussed.

2. Attention is drawn to familial instances of this disease and the rôle of genetic predisposition in its etiology.

3. The pathologic similarity of this disease to scleroderma of the lungs and to other collagen diseases is noted.

4. The use of ACTH and cortisone in the therapy of pulmonary fibrosis is discussed in the light of the clinical course of the disease as it is currently understood.

Acknowledgment

An expression of gratitude is due Dr. J. Ziskind, Chief of Pathology of the Veterans Administration Hospital, New Orleans, Louisiana, and to the medical staff of that hospital for kindly furnishing the clinical and pathologic data of case 2.

Summario in Interlingua

Le prime description de diffuse fibrosis pulmono-interstitial esseva presentate per Haman e Rich in 1944. Iste autores delineava le syndrome clinic de dyspnea, cyanosis, e corde pulmonal. Le subjacente pathologia pareva esser un extense hyperplasia del texitos conjunctive in le pulmones. Studios subsequente de iste syndrome ha presentate numerose etiologias, includente infectiones granulomatose, pneumonoconioses, e morbos de texito conjunctive como per exemplo periarteritis nodose, scleroderma, e lupus erythematose. Sequeva le conception que il se tracta in diffuse fibrosis del pulmones de un historesponsa general de ille organos.

Ben que numerose agentes etiologic ha essite describite, il es evidente que in un numero significative de patientes exhibiente le syndrome de Haman-Rich le causa remane incognoscite. Plure aspectos del syndrome idiopathic in le forma occurrente in le duo casos hic reportate merita nostre attention. Nos describe le constatationes clinic e pathologic, typic de idiopathic fibrosis pulmonar, que nos ha facite in le casos

de duo fratres e signala le existentia de un reporto del morbo in duo sorores. Il es remarcabile que le 30 publicate casos de iste relativemente infrequente morbo include duo pares de consanguineos. Le rolo de predisposition genetic in le formation de fibrosis pulmonar merita un serie consideration.

Le notion que le occurrentia acute es un characteristica essential del morbo debe esser corrigite. Il es un facto que le examine pathologic revela un considerabile quantitate de non-recente e ben-organisate dense texito conjunctive e etiam que le studio del historia del casos individual insimul con lor examine clinic revela frequentemente un insidiose e gradual comenciamento del morbo, durante que le acute e alarmante progression del symptomas es reservate al stadio pre-terminal. Recente reportos ha signalate le disastrose effectos de un reduction del dosage de ACTH o de cortisona in iste patientes, sed proque iste therapia es reservate pro le plus serie phases terminal del morbo, le conclusion mortal es possibilemente non un effecto del alteration del dosage steroide sed plus tosto simplemente un occurrentia coincidente con illo. Un del duo fratres in le presente reporto moriva post un reduction del doses exogene de ACTH; le altere moriva ben que ille recipeva constante e non-alterate doses del medication. Le longevitate del duo, mesurate super le base de stadios analoge de lor morbos, esseva quasi identic. Studios additional del therapia a steroides adrenal e a ACTH in diffuse fibrosis pulmono-interstitial es requirite.

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EDITORIAL

FIBRINOGEN DEFICIENCY

RECENT studies demonstrating fibrinogenopenia as the basic defect in a widely disparate group of hemorrhagic disorders have aroused renewed interest in this component of the coagulation mechanism. Included among these hemorrhagic disorders are the abnormal bleeding associated with some cases of abruptio placentae, amniotic fluid embolism, retention of a dead fetus in utero, carcinoma of the prostate with metastases, and pulmonary surgery. Interest has also been focused on the implications and applications of the fibrinolytic system which exists normally in the blood. A knowledge of some aspects of fibrinogen metabolism is fundamental to the understanding of these entities.

Fibrinogen, a globulin with a molecular weight of approximately 350,000, is formed in the liver. The normal plasma level is 200–400 mg.%. Recent physico-chemical studies [1] indicate that it is an asymmetrical molecule, resembling an ellipsoid approximately 750 Å in length and 38 Å in width. It contains carbohydrate corresponding to 3% reducing sugar (mannose and galactose) and 0.6% of hexosamine. X-ray diffraction studies reveal that its structure resembles the myosin-keratin group of proteins.

It seems clear that the action of thrombin on fibrinogen is of a proteolytic, enzymatic nature. The alteration of fibrinogen to fibrin, induced by thrombin, is accompanied by only a very slight, subtle change in chemical structure.[2] Thrombin splits off one or more peptides (fibrinopeptides) accounting for 3% of the protein nitrogen of fibrinogen. The molecules of thrombin-activated fibrinogen (F′) undergo spontaneous polymerization to form the fibrin clot. The fibrin monomers, thin rod-like structures, polymerize by sideways cohesion to form the fibrin strands of the clot. This process of aggregation continues for some time after the moment of gelation, the clotting time endpoint. Detailed studies have been made of the nature of the binding forces of the fibrin monomers [3] but these will not be discussed here. The fibrin clot is essentially a three dimensional network of protein strands in the interstices of which large amounts of fluid can be held. Subsequent retraction of the clot is thought to occur as a result of the fusion of platelets which are firmly fixed to the fibrin strands. The further action of thrombin is inhibited by a series of antithrombin reactions.

The formation of the fibrin clot must be viewed as only one of a group of reactions concerned with hemostasis. It may not even be the most important. There is considerable evidence that platelet agglutination and

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[2] Lorand, L.: Interaction of thrombin and fibrinogen, Physiol. Rev. 34: 742, 1954.
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vasoconstriction are perhaps of greater importance in terminating capillary bleeding. Thus even in the total absence of fibrinogen, as in congenital afibrinogenemia, hemostasis can occur. Fibrin formation is probably essential for more permanent hemostasis. Biggs and Macfarlane[4] suggest that the complexity of the coagulation mechanism, with its activators and inhibitors, derives from the necessity to limit coagulation to the injured area and to guard against disastrous thrombosis of important vessels.

Clinical investigation of patients with congenital afibrinogenemia has afforded an opportunity to study other aspects of fibrinogen metabolism. Alexander et al.[5] found that the various steps leading to the evolution of thrombin occurred in the absence of fibrinogen just as they do normally. Thus, platelets underwent agglutination and lysis; prothrombin consumption occurred with even greater rapidity; anti-hemophilic factor and proaccelerin (Ac-globulin, Factor V) disappeared and proconvertin (SPCA, Factor VII) was transformed to convertin. In other words, the blood of these patients underwent "chemical coagulation" even though it remained fluid. Gitlin and Borges[6] in studying the same patients, found that approximately half the injected fibrinogen, administered in the form of Fraction I (Cohn), disappeared extravascularly in two days and could be demonstrated in the connective tissue of skin and muscle biopsies. The half-life of the injected fibrinogen was approximately four days. These studies cast some light on the equilibrium between intra- and extravascular fibrinogen. Pinniger and Prunty[7] and others found that a significant change in clotting efficiency could be demonstrated at a plasma fibrinogen level of 60 mg.% although as little as 20 to 30 mg.% still permitted the formation of apparently normal clots showing good retraction. Amounts less than this gave friable and fragmentary clots.

Normal blood contains a mechanism for the dissolution of clots.[8] When collected and stored under aseptic conditions in vitro clotted blood undergoes fibrinolysis in a matter of days or weeks. In certain experimental and clinical situations dissolution of blood clot may occur within a few minutes to several hours. At times this activity may be so marked that a hemorrhagic diathesis results. Although many hypotheses exist, the physiologic significance of this phenomenon is obscure. One obvious possibility is that it may function normally to keep the vascular bed free of thrombi which may be

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formed under certain conditions. The removal of blood clot after its period of usefulness is over has also been suggested as a function.

As with most other phases of coagulation, fibrinolysis is the resultant of a system of checks and balances. An inactive enzyme precursor, plasminogen, exists normally in blood.[9] When activated, the enzyme is termed plasmin. Evidence exists also for the presence of an inhibitor, antiplasmin. Fibrinolytic activity may be accentuated by the activation of plasminogen or the disruption of the plasmin-antiplasmin equilibrium. By electrophoretic fractionation it can be shown that plasmin is associated with the globulins, more specifically Fraction III—2–3 (Cohn), and that antiplasmin is associated with albumin. Various tissues have also been found to possess fibrinolytic activity. Of all those studied it is of interest to note that lung extracts had the greatest activity, at times exceeding that of blood. There is some doubt as to whether tissue fibrinolysins are separate and distinct from plasmin or whether, as Astrup and Permin [10] suggest, they contain an activator of plasminogen which they term fibrinokinase.

In vitro, plasminogen can be activated by the treatment of serum with chloroform and by the use of culture filtrates of certain beta hemolytic streptococci.[11] The former is believed to remove antiplasmin thereby unmasking the lytic enzyme. Streptococcal filtrates apparently contain an enzyme capable of activating plasminogen. This enzyme is known as streptokinase.

Very little is known of the mechanisms involved in the activation of plasminogen in vivo. Increased fibrinolytic activity has been observed in a variety of clinical and experimental situations. Tagnon et al.[12] demonstrated increased activity in hemorrhagic shock and burns. Westphal et al.[13] noted a similar occurrence after the induction of tourniquet shock. Fantl and Simon [14] found increased fibrinolytic activity after electrically induced convulsions. In a series of studies, Macfarlane and coworkers [15] noted elevated fibrinolysis in surgical patients. It was concluded that the nature of the operation, the anesthetic, and the degree of trauma showed little or no correlation with the fibrinolytic activity of the serum. A common denominator appeared to be anxiety. This conclusion is supported by the observations of Latner [16] on individuals during air raids, with anxiety

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[12] Tagnon, H. J., Levenson, S. M., Davidson, C. S., and Taylor, F. H. L.: The occurrence of fibrinolysis in shock, with observations on the prothrombin time and the plasma fibrinogen during hemorrhagic shock, Am. J. M. Sc. **211**: 88, 1946.

[13] Westphal, U., Kocholaty, W., McDonald, B., King, E., and Jensen, H.: Studies on proteolytic, fibrinolytic, antitryptic and antifibrinolytic activities in the blood of rats, Proc. Soc. Exper. Biol. and Med. **75**: 862, 1950.

[14] Fantl, P., and Simon, S. E.: Fibrinolysis following electrically induced convulsions, Australian J. Exper. Biol. and M. Sc. **26**: 521, 1948.

[15] Macfarlane, R. G., and Biggs, R.: Observations on fibrinolysis: spontaneous activity associated with surgical operations, trauma, etc., Lancet **2**: 862, 1946.

[16] Latner, A. L.: Anxiety as a cause of fibrinolysis, Lancet **1**: 194, 1947.

states, and in students taking examinations. Truelove [17] also observed increased fibrinolysis in patients receiving alarming suggestions under hypnosis. In very few instances, however, is fibrinolysis so active as to produce a hemorrhagic syndrome. Increased fibrinolytic activity may, however, be an accessory mechanism in the hemorrhagic syndromes associated with hypofibrinogenemia. Further comment will be made on this below. There is some evidence that the plasmin-antiplasmin equilibrium may be influenced by pituitary and adrenal hormones.[18]

Afibrinogenemia and hypofibrinogenemia may occur either as a hereditary or an acquired disorder. The former is quite rare. Prichard and Vann [19] in reviewing the literature were able to find reports of only 21 cases, excluding their own, since the original case of Rabe and Salomon in 1920. Studies in these patients indicate that the basic defect is an inability to synthesize significant amounts of fibrinogen. Despite the fact that the coagulation time is indefinitely prolonged, clinical symptoms are often less severe than in hemophilia. Fifteen of the 22 reported cases occurred in males. In seven there was a history of consanguineous marriage in the parents or grandparents. In four instances hypofibrinogenemia was found in one or more relatives. Bleeding was often noted in infancy and occurred with the eruption of teeth, minor traumata, and in association with surgery. Some patients have shown concomitant thrombocytopenia. The bleeding time was prolonged in some instances and normal in others. Despite the absence of fibrinogen, the healing of wounds occurred normally. As would be expected, the erythrocyte sedimentation rate is low. The prognosis is poor with the oldest survivor in the group of 22 being 20 years old. Replacement therapy with either whole blood or fibrinogen is the only effective approach to management. No instance of acquired resistance to repeated infusion of fibrinogen has been noted. Lewis and Ferguson [20] studied one patient for evidence of excessive fibrinolysis and failed to demonstrate it.

Acquired afibrinogenemia or hypofibrinogenemia occurs with considerably greater frequency than the congenital variety. The occurrence of hypofibrinogenemia with acute yellow atrophy of the liver is so well known as to require very little comment. Isolated instances of hypofibrinogenemia have been reported in association with polycythemia vera, pernicious anemia, and acute granulocytic leukemia.[21, 22] Of particular interest have been recent reports of fibrinopenia associated with a severe hemorrhagic disorder

[17] Truelove, S. C.: Fibrinolysis and the eosinophil count, Clin. Sc. **10**: 229, 1951.

[18] Ungar, G.: Thrombosis and stress: role of the fibrinolytic system, Proc. Int. Conf. on Thrombosis and Embolism, 1954, Benno Schwabe and Co., Basle, p. 421.

[19] Prichard, R. W., and Vann, R. L.: Congenital afibrinogenemia: report on a child without fibrinogen and review of the literature, Am. J. Dis. Child. **88**: 703, 1954.

[20] Lewis, J. H., and Ferguson, J. H.: Afibrinogenemia: report of a case, Am. J. Dis. Child. **88**: 711, 1954.

[21] Bjorkman, S. E.: Three cases of polycythemia with fibrinopenia, Acta med. Scandinav. **129**: 472, 1948.

[22] Cooperberg, A. A., and Neiman, G. M. A.: Fibrinogenopenia and fibrinolysis in acute myelogenous leukemia, Ann. Int. Med. **42**: 706, 1954.

occurring as a complication of various mishaps of pregnancy, in carcinoma of the prostate, and in association with pulmonary surgery. These will be considered in somewhat more detail.

Virtual defibrination of the circulating blood can be produced in vivo by the intravenous infusion of tissue thromboplastin.[23, 24, 25] Experimentally, it has been shown that the rapid injection of thromboplastin is lethal and will be found to be associated, at autopsy, with large clots in the pulmonary artery, inferior vena cava and portal vessels. If the injection is gradual, complete defibrination may occur without obvious harm to the animal. Several hours after the infusion is complete, in the latter instances, the concentration of fibrinogen begins to rise and in 24 hours, the level may be higher than before the injection. Human placental tissue and amniotic fluid are highly thromboplastic in vitro and are capable of producing intravascular defibrination in experimental animals. There is a striking resemblance between these experimental situations and the serious, and often fatal, hemorrhagic diathesis known to occur in some patients with premature separation of the placenta, amniotic fluid embolism, and intrauterine retention of a dead fetus.

Premature separation of the placenta, a complication arising at or near the time of parturition, is a not uncommon mishap of pregnancy. Its reported incidence varies in different series from 1 in 85 to 1 in 250 deliveries. Dieckmann [26] was the first to recognize that the generalized hemorrhagic diathesis associated with abruptio placentae was due to hypofibrinogenemia. Patients display profuse uterine hemorrhage, subcutaneous ecchymoses, epistaxis, hematuria, melena, gingival bleeding and bleeding at the sites of venapuncture or parenteral injections. Shock may supervene and the condition may be rapidly fatal. At autopsy intravascular fibrin deposits may be seen, particularly in the lungs, kidneys and liver. The diagnosis can be established by quantitative fibrinogen determination or more rapidly, in a semiquantitative fashion, by the effect of topical thrombin solution on the blood. If there is complete afibrinogenemia no clot will form even in the presence of thrombin. With hypofibrinogenemia, the clotting time may be normal but the clot will be small and flabby. On observation, it will be noted that the red cells tend to separate from the clot leaving a tiny nubbin of clot. In some instances, and perhaps due to the associated shock, fibrinolysis may also be shown to be unusually active. Clearer understanding of the pathophysiologic mechanisms involved has resulted in more rational therapy with the consequent saving of many lives. The principles of therapy include treatment of shock by whole blood transfusions, intravenous fibrinogen in

[23] Copley, A. L.: Studies on human placental thromboplastin in vitro and in vivo, Science 101: 436, 1945.

[24] Schneider, C. L.: Complications of late pregnancy in rabbits induced by experimental placental trauma, Surg., Gynec. and Obst. 90: 613, 1950.

[25] Ratnoff, O. D., and Conley, C. L.: Studies on afibrinogenemia. II. Defibrinating effect of dog blood on intravenous injection of thromboplastic material, Bull. Johns Hopkins Hosp. 81: 1, 1947.

[26] Dieckmann, W. J.: Blood chemistry and renal function in abruptio placentae, Am. J. Obst. and Gynec. 31: 734, 1937.

doses of 4 gm. or more, and prompt emptying of the uterus if this has not already occurred.

Amniotic fluid emboli may enter the maternal circulation before, during, or after childbirth. In some such cases severe respiratory distress, dyspnea and cyanosis occur leading rapidly to death. In other instances patients gradually slip into shock a few hours post partum and exhibit widespread hemorrhagic phenomena. In addition to hypofibrinogenemia, some of these patients exhibit thrombocytopenia and hypoprothrombinemia. Treatment is essentially similar to that noted above.

Fetal death in utero with retention of the fetus occurring after the fourth month of gestation and due to a variety of causes including Rh iso-immunization, may be associated with hypofibrinogenemia and a hemorrhagic diathesis. The mechanism of action is believed to be the absorption of thromboplastic material from either the dead fetus, the placenta or amniotic fluid. The possibility of excessive fibrinolytic action has also been considered. Usually fibrinogenopenia occurs after the dead fetus has been retained for at least five weeks. The incidence of hypofibrinogenemia in such cases appears to be fairly high. Ratnoff et al.[27] noted this phenomenon in eight of 31 cases of retained dead fetus and Weiner et al.[28] in three of 15 patients. Improvement follows emptying of the uterus.

In 1930, Jurgens and Trautwein [29] reported the case of a patient with carcinoma of the prostate and extensive metastases who developed a severe hemorrhagic disorder apparently due to fibrinogenopenia. This remained an isolated observation until quite recently when a number [30, 31, 32, 33] of similar reports began to appear in the literature. Huggins and Vail,[34] in 1943, demonstrated that prostatic tissue contains an enzyme capable of digesting fibrinogen and fibrin. Tagnon et al.[32] demonstrated increased fibrinolytic activity of the blood in several patients with carcinoma of prostate of a degree sufficient to produce fibrinogenopenia and serious hemorrhage. These workers believe that prostatic fibrinolysin enters the blood in a manner analogous to acid phosphatase in this disease. In a group of 48 patients with malignant disease of the prostate they found six who demonstrated in-

[27] Ratnoff, O. D., Lauster, C. F., Sholl, J. G., and Schilling, M. O.: Hemorrhagic state during pregnancy with presence of maternal Rh antibodies, death of fetus and hypofibrinogenemia, Am. J. Med. **13**: 111, 1952.

[28] Weiner, A. E., Reid, D. E., Roby, C. C., and Diamond, L. K.: Coagulation defects with intrauterine death from Rh isosensitization, Am. J. Obst. and Gynec. **60**: 1015, 1950.

[29] Jurgens, R., and Trautwein, H.: Ueber Fibrinopenie (Fibrinogenopenie) beim erwachsenen nebst Bemerkungen über die Herkunft des Fibrinogens, Deutsch. Arch. f. klin. Med. **169**: 28, 1930.

[30] Marder, M., Weiner, M., Shulman, P., and Shapiro, S.: Afibrinogenemia occurring in a case of malignancy of the prostate with bone metastases, N. Y. State M. J. **49**: 1197, 1949.

[31] Seale, R. A., Jampolis, R. W., and Bargen, J. A.: Clotting defect in the presence of metastatic carcinoma of the prostate: case report, Surg. Clin. N. A. **31**: 1111, 1951.

[32] Tagnon, H. J., Whitmore, W. F., and Shulman, N. R.: Fibrinolysis in metastatic cancer of the prostate, Cancer **5**: 9, 1952.

[33] Crane, J. J., Ware, A. G., and Hamilton, J.: Spontaneous afibrinogenemia in cancer of the prostate: report of two cases, Trans. West. Sect. Am. Urol. A. **21**: 65, 1954.

[34] Huggins, C., and Vail, V. C.: Plasma coagulation and fibrinogenolysis by prostatic fluid and trypsin, Am. J. Physiol. **139**: 129, 1943.

creased fibrinolytic activity on one or more occasions.[35] Among the remaining 42 there were 31 with metastatic lesions but no evidence of fibrinolysis. The reason for the apparent random occurrence of this phenomenon is unknown. More extensive study is obviously indicated. Although an acute hemorrhagic episode might be benefited by the administration of fibrinogen, a more rational, and perhaps more permanent, result can be achieved by the administration of estrogens and/or orchiectomy.

As previously mentioned, extracts of pulmonary tissue have been found to exhibit marked fibrinolytic activity. It is not surprising, therefore, in this era of extensive pulmonary surgery that occasional reports have begun to appear in the literature of a serious hemorrhagic disorder accompanying operative manipulation of the lung.[36, 37] Whether the severe fibrinogenopenia found in these cases is the result of excessive fibrinolysis or of intravascular defibrination by tissue (lung) thromboplastin remains to be determined. Penn and Walker[37] have recently described two patients who developed a hemorrhagic diathesis following lobectomy for bronchiectasis. In both instances the bleeding phenomena occurred two and one-half to four hours following surgery. One patient died of hemorrhagic shock despite the administration of fibrinogen. The other received a total of 10,000 c.c. of whole blood and 8 gm. of fibrinogen and survived. No systematic study of the incidence of this entity or of the factors responsible for its occurrence has yet been reported in the literature.

Although major interest has centered upon the deleterious consequences of intravascular defibrination and hyperactivity of the fibrinolytic system, the possibility of manipulating the plasminogen-antiplasmin equilibrium for therapeutic purposes has also engaged the interest of various workers in recent years. The effect of activation of plasminogen by the injection of streptokinase and streptococcal desoxyribonuclease (streptodornase) into exudates in various bodily cavities has been studied by several groups of investigators.[38, 39] The clinical response is dependent to some extent upon the plasminogen content of these fluids. Results have been variable. A more direct approach has been employed recently, i.e., the intracavitary and intravascular injection of human plasmin. Grossi et al.[40] demonstrated that human plasmin was effective in producing intravascular lysis of sodium

[35] Tagnon, H. J., Whitmore, W. F., Schulman, P., and Kravitz, S. C.: The significance of fibrinolysis occurring in patients with metastatic cancer of the prostate, Cancer **6**: 63, 1953.

[36] Soulier, J. P., Mathey, J., Bolloch, A. G. Le, Daumet, P., and Fayet, H.: Syndromes hemorragiques mortels avec incoagulabilité totale par défibrination et avec fibrinolyse, Rev. d'hémat. **7**: 30, 1952.

[37] Penn, S. R., and Walker, J. H.: Defective blood coagulation following pulmonary surgery, N. England J. Med. **250**: 764, 1954.

[38] Tillett, W. S., and Sherry, S.: The effect in patients of streptococcal fibrinolysin (streptokinase) and streptococcal desoxyribonuclease on fibrinous, purulent and sanguineous pleural exudations, J. Clin. Investigation **28**: 173, 1949.

[39] Cathie, I. A. B.: Bacterial fibrinolysin, its possible therapeutic application in tuberculous meningitis, J. Clin. Path. **2**: 73, 1949.

[40] Grossi, C. E., Cliffton, E. E., and Cannamela, D. A.: The lysis of intravascular thrombi in rabbits with human plasmin (fibrinolysin), Blood **9**: 310, 1954.

morrhuate-induced thrombi in the marginal ear veins of rabbits where the thrombus was less than 24 hours old. Partial or total lysis occurred with thrombi over 24 hours old. Lysis took place within one to two hours after the injection of plasmin. Similar results were noted in dogs. Another approach to the problem of inducing controlled fibrinolysis has been by the diminution of antiplasmin activity of serum in vivo. Fibrinolytic therapy of thrombotic disease appears to be a promising area for investigation. An evaluation of its clinical utility must await further study.

MILTON S. SACKS, M.D.

REVIEWS

Textbook of Biochemistry. 2nd Ed. By EDWARD STAUNTON WEST, Ph.D., and WILBERT R. TODD, Ph.D., Professors of Biochemistry, University of Oregon, School of Medicine, Portland, Oregon. 1356 pages; 16 × 24.5 cm. The Macmillan Company, New York, N. Y. 1955. Price, $12.00.

The 1954 and 1955 years have been favored by the appearance of several excellent textbooks on biochemistry. This literary productivity exemplifies the wide interest and extensive advances in this discipline—especially in the fields of medicine, agriculture, pharmacy, and industry. The first edition of the book under review appeared in 1951. Scientists everywhere praised the comprehensive, up-to-date treatment of this dynamic field in which new information is being accumulated at a phenomenal rate. Many teachers of biochemistry, especially in medical schools, adopted it for their classes.

This volume tends to follow the classical division of subject matter usually found in biochemistry textbooks. The various topics covered and the number of pages devoted to each topic are as follows: physical chemistry as applied to biochemical systems, 149; carbohydrate, fat, and protein chemistry, 262; enzymes and digestion, 114; blood and body fluids including respiration, acid-base balance, and water and electrolyte equilibrium, 155; vitamins and metabolism, 553; urine, 35; and hormones, 38 pages, respectively. Thus special emphasis is placed upon physical chemistry, intermediary metabolism, and body fluids. The formation and composition of urine and the chemistry and action of hormones are treated in a concise and rather cursory manner (70 pages).

Each of the 32 chapters has been revised by the authors. The chapters dealing with metabolism have been rewritten to conform with the rapid advances in this field. Our knowledge concerning purine and porphyrin metabolism, hydrochloric acid secretion, vitamins and coenzymes, the chemistry of vision and of ossification, photosynthesis, and metabolic antagonism has been revised in the light of recent findings.

According to the authors the principles of biochemistry related to medicine have been given special attention. Little emphasis, however, has been placed on subjects generally included under the term "clinical chemistry." This omission could readily be corrected in future editions. Physicians, students, and workers in the field of science can obtain a sound, comprehensive, authoritative, up-to-date picture of modern biochemistry from this excellent book.

The book is well produced, clearly written, and each chapter documented with an extensive bibliography. It contains an excellent index. The addition of photographs and more illustrations would enliven the text. While the authors are to be congratulated for a job well done, they should be warned that new editions of this excellent book will be expected at frequent intervals.

E. G. S.

Hematology. 2nd Ed. By CYRUS C. STURGIS, M.D., Professor of Internal Medicine, Chairman of the Department of Internal Medicine, University of Michigan Medical School, and Director of the Thomas Henry Simpson Memorial Institute for Medical Research, University of Michigan, Ann Arbor, Michigan. 1,222 pages; 16.5 × 26.5 cm. Charles C Thomas, Springfield, Illinois. 1955. Price, $19.50.

The rapid pace of new developments in the wide field of blood disorders quickly makes a text obsolete, unless it is frequently revised. This second edition of Dr.

Sturgis' textbook is remarkably complete in its coverage of recent contributions applicable to clinical hematology. At the same time, there has been no sacrifice of the interesting and desirable historical information relative to the topics discussed. The text pertains to clinical situations and does not give descriptions of laboratory technics nor interpretation of results.

The author writes clearly and presents the material in a most readable manner, calling freely upon his own extensive experience to supplement and illustrate. Most subjects are discussed in fine detail, which accounts for the length of the volume. An extensive bibliography follows each chapter and includes references spanning the time from the original description to the very recent works. There are sections of the book devoted to the anemias, hemorrhagic states, leukemias, lymphomas, infectious mononucleosis, agranulocytosis, polycythemia, the lipoidoses, blood transfusion and blood substitutes. This valuable text would be an asset to any medical library and would be of interest to anyone seeking basic information and blood bibliography pertaining to the clinical aspects of hematology.

A. B.

Modern Trends in Blood Diseases. Edited by JOHN F. WILKINSON, M.D., M.Sc., Ph.D., F.R.C.P., F.R.I.C., Consultant Physician, United Manchester Hospitals; Director, Department of Haematology, Manchester Royal Infirmary; Reader in Haematology and Lecturer in Medicine, University of Manchester. 359 pages; 17.5 × 25 cm. Paul B. Hoeber, Inc., Medical Book Department of Harper & Bros., New York. 1955. Price, $12.00.

This book was not compiled as a basic text in hematology, but rather as a guide to some of the more recent results and trends in both clinical and laboratory investigations in the broad field of blood diseases. The subjects chosen are diverse but all pertinent to today's practice of medicine. The text includes matters that range from purely clinical to wholely theoretical. Outstanding persons have been chosen to write each section, and the material is uniformly well written and clearly presented. The contents include sections on bone changes and blood diseases, hematologic technics, dermatological aspects of blood diseases, pediatric hematology, studies on iron metabolism, blood pigments, hemolytic anemia, anemia of infection, changes in the fundus in diseases of the blood, chronic leukemias, acute leukemias, anticoagulant therapy, vitamin B_{12}, isoimmunization to blood group antigens, and the reticuloses. Each chapter closes with a large bibliography.

As is seen from the contents, the book contains an interesting array of material, all of which is not usually found in a single volume. It would be of particular interest to anyone in clinical or investigative hematology, but also of more than passing interest to any physician who is apt to encounter hematologic disorders.

A. B.

Cardiovascular Surgery. By GERALD H. PRATT, M.D., F.A.C.S., Associate Clinical Professor of Surgery, New York University College of Medicine. 843 pages; 24 × 15.5 cm. Lea and Febiger, Philadelphia. 1954. Price, $15.00.

The author's stated purpose for writing this book was to provide surgeons, internists and students with a summary of accepted or acceptable surgical treatment for cardiovascular lesions.

The book is extremely wide in scope. It is divided into nine sections. Some of the material which is isolated into separate sections and sometimes overlaps would be more meaningful if integrated into the more general subject matter.

The illustrations are excellent and, in most instances, enhance the explanations. An ample bibliography is provided.

The author has drawn freely from his own vast clinical experience. Because of this, other experienced readers will occasionally find statements which may seem controversial. There are numerous coined words which season the author's style of writing.

The book supplies considerable clinical and surgical information and adequately covers a vast field. Closer editing would improve the entire book.

R A. C.

Surgery of the Heart. By CHARLES P. BAILEY, M.D., M.Sc. (Med.), LL.D. (Hon.) F.A.C.S., F.C.C.P., F.I.C.S., Professor and Head of the Department of Thoracic Surgery, Hahnemann Medical College and Hospital, Philadelphia, Pa. 1,062 pages; 24 × 15.5 cm. Lea and Febiger, Philadelphia. Price, $25.00.

Dr. Bailey has compiled into one volume apparently all that is currently known about cardiac surgery.

The book is divided into three parts. The first part outlines the development of cardiac surgery, the types of anesthesia used for cardiac surgery and various cardiac surgical technics. The second part of the book covers all aspects of congenital heart disease, whereas the third part covers all aspects of acquired heart disease. Both of the latter parts include complete surgical treatment.

The author has had much experience in the field of cardiac surgery and he has drawn considerably from this experience. Many of the procedures discussed are not yet accepted. This is hardly a remarkable feature in a book attempting to cover such a rapidly expanding branch of surgery.

The drawings are overly simplified and, therefore, detract from an otherwise fine book.

This book is recommended for everyone interested in cardiac surgery from both the theoretical as well as the practical viewpoint.

R A. C.

Practical Management of Disorders of Liver, Pancreas, and Biliary Tract. By JOHN R. TWISS, M.D., F.A.C.P., and ELLIOT OPPENHEIM, M.D., F.A.C.P. 653 pages; 15.5 × 24 cm. Lea and Febiger, Philadelphia. 1955. Price, $15.00.

This is a book which was written to be a practical guide. The authors are clinicians—the physicians and surgeons of the Medical and Surgical Biliary Tract Clinic of the New York University Hospital, which was founded in 1929. Fundamentally this book represents the important accumulated information in this Clinic over a span of 26 years.

The emphasis of the book has been on diagnostic procedures and methods of management in an effort to obtain specific diagnoses and to utilize the indicated forms of therapy. As a rule, medical therapy in these disorders has been discussed at length. Similarly, surgical principles and the indications for surgery have been fully discussed. Fortunately, details of surgical procedures have been omitted.

The book has been divided into five sections: (1) General considerations; (2) disorders of the gallbladder and extra-hepatic biliary tree; (3) disorders of the liver; (4) disorders of the pancreas; and (5) appendix (technical procedures).

The portion of section one which deals with history seems inadequate. The major symptom discussed is pain and very little more. The handling of the physical examination seems only fair, with some important omissions. The enumeration of causes for a physical finding—such as splenomegaly—copied from a textbook of differential diagnosis is unimpressive.

The section dealing with disorders of the gallbladder and extra-hepatic biliary tree seems by far the best portion of the book. Here the long, careful, detailed clinical experience of the authors is pleasantly evident. On might take issue with the

recommended management of the typhoid carrier state, in which cholecystectomy within six months of the acute illness is said to have "cured' 68% of the patients of the carrier state.

The section dealing with disorders of the liver is very good, concise, and clear. In the discussion of Weil's disease, no mention is made of culture or animal inoculation of the blood or urine for leptospira. The recommended diagnostic procedure is a dark-field examination of the blood.

In the section concerned with disorders of the pancreas, which are difficult at best, the authors do very well until discussing the chronic diseases of the pancreas where they approach the problem from the viewpoint of simply listing etiologic factors, symptomatologic types, and attempts at diagnosis of chronic pancreopathies. The functional classification is also poor and uninstructive. Nevertheless, despite a poor description of the chronic diseases of the pancreas, the description of the management of chronic pancreatic disease is excellent.

The last section of the book—the appendix—contains detailed directions for clinical and laboratory procedures with an enumeration of normal values and excellent bibliographic references for technics.

In summary, this book is what its authors intended it to be, a practical clinical guide. It emphasizes clearly to the reader the points which they intended to emphasize. The valuable information, advice, and suggestions concerning management of clinical problems within this sphere are excellent and far outweigh the relatively minor criticisms which have been enumerated above.

W. C. E.

Pathology for the Surgeon. 7th Ed. By WILLIAM BOYD, M.D., Edin.; Dipl. Psychiat. Edin.; F.R.C.S. Canada; F.R.C.P. London; M.R.C.P. Edin.; F.R.S. Canada; LL.D. Sask.; D.Sc. Man.; M.D. Oslo; Lecturer on the Humanities in Medicine, The University of Toronto, Visiting Professor of Pathology, The University of Alabama. 737 pages; 18 × 26 cm. W. B. Saunders Company, Philadelphia. 1955. Price, $12.50.

This book presents a refreshing new look into the field of surgical pathology. The author writes with the refined simplicity of a scholar and the didactic style of a lecturer. The 34 chapters comprising the text are arranged according to system and are coherently presented.

Each chapter is prefaced by a short outline of the content found therein. The subject matter is well covered by description and clinical correlation. Well executed photomicrographs and gross pictures lend support to the written text. At the end of each chapter there is a current well chosen list of references for additional reading.

The reviewer enthusiastically recommends this text to the surgeon, and also to the internist. It is a valuable addition to the library of the resident in surgery and an excellent reference for the practicing surgeon. Needless to say the pathologist would also profit from this text.

L. K.

BOOKS RECENTLY RECEIVED

Books recently received are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

Advances in Internal Medicine. Volume VII, 1955. Editors: WILLIAM DOCK, M.D., Long Island College of Medicine, Brooklyn; and I. SNAPPER, M.D., Beth-El Hospital, Brooklyn. 311 pages; 23.5 × 15.5 cm. 1955. The Year Book Publishers, Inc., Chicago. Price, $8.50.

The Body Fluids: Basic Physiology and Practical Therapeutics. By J. RUSSELL ELKINTON, M.D., and T. S. DANOWSKI, M.D. 626 pages; 23.5 ×15.5 cm. 1955. The Williams & Wilkins Company, Baltimore. Price, $10.00.

Casimir Funk: Pioneer in Vitamins and Hormones. By BENJAMIN HARROW. 209 pages; 21.5 × 14.5 cm. 1955. Dodd, Mead & Company, New York. Price, $4.00.

Chemotherapy of Malaria. World Health Organization Monograph Series No. 27. By SIR GORDON COVELL, C.I.E., M.D., Adviser on Malaria, Ministry of Health, Director, Malaria Laboratory, Horton Hospital, Epsom, Surrey, England; G. ROBERT COATNEY, Ph.D., Laboratory of Tropical Diseases, National Microbiological Institute, National Institutes of Health, Bethesda, Md., USA; JOHN W. FIELD, C.M.G., M.D., Director, Institute for Medical Research, Kuala Lumpur, Federation of Malaya; and JASWANT SINGH, M.B., Ch.B., D.P.H., D.T.M. & H., Director, Malaria Institute of India, Delhi, India. 123 pages; 24 × 16 cm. 1955. World Health Organization, Geneva; available in U.S.A. from Columbia University Press, International Documents Service, New York. Price, $3.25.

Counseling in Medical Genetics. By SHELDON C. REED, Director, Dight Institute for Human Genetics, The University of Minnesota. 268 pages; 20.5 × 14 cm. 1955. W. B. Saunders Company, Philadelphia. Price, $4.00.

Embryologie: Ein Lehrbuch auf Allgemein Biologischer Grundlage. By DIETRICH STARCK. 688 pages; 26.5 × 18.5 cm. 1955. Georg Thieme Verlag, Stuttgart; available in U.S.A. from Intercontinental Medical Book Corporation, New York. Price, $18.55.

The Hemorrhagic Disorders: A Clinical and Therapeutic Approach. By MARIO STEFANINI, M.D., Associate Professor of Medicine, Tufts University School of Medicine, etc.; and WILLIAM DAMESHEK, M.D., Professor of Medicine, Tufts University School of Medicine, etc. 368 pages; 26 × 17.5 cm. 1955. Grune & Stratton, New York. Price, $11.75.

Human Physiology. 4th Ed. By F. R. WINTON, M.D., D.Sc., Professor of Pharmacology, University College London; and L. E. BAYLISS, Ph.D., Honorary Research Associate in Physiology, University College London. 616 pages; 24.5 × 16 cm. 1955. Little, Brown & Company, Boston. Price, $3.00.

J. A. M. A. Clinical Abstracts of Diagnosis and Treatment. (Published with the Approval of the Board of Trustees, American Medical Association.) 627 pages; 22.5 × 14 cm. 1955. Intercontinental Medical Book Corporation with Grune & Stratton, Inc., New York and London. Price, $5.50.

Joint ILO/WHO Committee on the Hygiene of Seafarers: Second Report. World Health Organization Technical Report Series No. 92. 20 pages; 24 × 16 cm. (paper-bound). 1955. World Health Organization, Geneva; available in U.S.A. from Columbia University Press, International Documents Service, New York. Price, 30 cents.

The Josiah Macy, Jr. Foundation, 1930–1955: A Review of Activities. 174 pages: 24 × 16 cm. 1955. The Josiah Macy, Jr. Foundation, New York. Complimentary.

Nutrition Practices: A Guide for Public Health Administrators. 72 pages; 2³ × 15 cm. (paper-bound). 1955. American Public Health Association, New York. Price, $1.00 per copy, 75¢ per copy in quantities of 25 or more.

Old Age in the Modern World: Report of the Third Congress of the International Association of Gerontology, London, 1954. 647 pages; 22.5 × 14.5 cm. 1955. The Williams & Wilkins Co., Baltimore. Price, $8.00.

Palpacion Abdominal: Semiotecnia y Valor Semiologico. By PEDRO C. ROSPIDE. 179 pages; 23 × 16.5 cm. (paper-bound). 1955. Lopez & Etchegoyen, S.R.L., Buenos Aires, Argentina.

The Physician and the Law. By ROWLAND H. LONG, Member Massachusetts and New York Bars, Lecturer in Forensic Medicine, New York University Post-Graduate Medical School; foreword by MILTON HELPERN, M.D., Chief Medical Examiner, New York City. 284 pages; 21.5 × 14.5 cm. 1955. Appleton-Century-Crofts, Inc., New York. Price, $5.75.

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